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CUTANEOUS INNERVATION

AN EXPERIMENTAL STUDY

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The nature and significance of the sensory phenomena resulting from cutaneous denervation have been subjects of much controversy among neurologists and psychologists. These phenomena—first studied systematically by Rivers and Head [1]—constitute the principal factual basis of Head's well known theory that the skin is innervated by two systems of afferent nerve fibers, called by him the protopathic and the epicritic. Head advanced this hypothesis in opposition to the traditional view which held that cutaneous sensitivity depends on the activities of four specific types of sensorineural mechanisms corresponding to the four psychologic "qualities" of touch, pain, cold and warmth. Head considered such a theory inadequate to account either for the patterns of dissociation produced by denervation or for the peculiar alterations in the character of the sensations elicited in such areas. Accordingly he proposed a dynamic theory patterned after Hughlings Jackson's doctrine of evolutionary levels of nervous organization. Two systems of cutaneous nerve fibers were postulated, the activities and interrelations of which accounted for all cutaneous phenomena. Head considered the protopathic system—responsive to prick, to stimulation of hair and to extremes of thermal stimuli—to be a primitive reflex mechanism, mediating an explosive, "all-or-nothing" type of response when acting in isolation. The epicritic system was considered as being sensitive to

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This paper was read in substance in the symposium on sensation at the Fifteenth Annual Meeting of the Association for Research in Nervous and Mental Diseases, New York, Dec. 28, 1934. Dr. R. S. Cunningham, Professor of Anatomy at the Vanderbilt University School of Medicine, suggested the problem and provided the facilities for the experimental work. Dr. Barney Brooks, Professor of Surgery at the Vanderbilt University School of Medicine, performed all the operations involved in the experiment. Dr. Brooks was assisted by Dr. Cobb Pilcher.

1. Rivers, W. H. R., and Head, Henry: A Human Experiment in Nerve Division, Brain **31**:323, 1908.

light contact, to intermediate grades of thermal stimuli and to the size, shape and relative location of stimuli. The epicritic system was regarded as a later phylogenetic acquisition and, according to Head, served to inhibit the abnormal intensity of sensation and the faulty localization characteristic of the protopathic level of nervous activity.

Head based his theory on the following experimental observations: (1) the dissociation of protopathic sensitivity from epicritic in the intermediate zone surrounding an anesthetic area; (2) the presence of epicritic sensitivity, dissociated from protopathic, in a small triangular area on Head's wrist; (3) the earlier return of protopathic sensitivity during nerve regeneration; (4) abnormally intense sensations and faulty localization in all the areas in which protopathic sensitivity occurred in isolation. The denervation experiment has been repeated by Trotter and Davies,[2] by Boring [3] and by Schafer.[4] All these investigations resulted in disagreement with Head's theoretical position, and in each of them factual discrepancies were reported. Carr [5] subjected Head's work to a searching analysis, in terms of the consistency of both fact and theory, in the light of Trotter and Davies' results. He concluded that if mere dissociation were the criterion of discreteness of neural mechanisms, Head's results would more logically require seven than two systems. Cobb [6] reviewed the work of Head, of Trotter and Davies, of Boring and several clinical studies of injuries to peripheral nerves and concluded that Head's hypothesis was not supported by the later studies. Cobb presented also a review of the results of his examinations in cases of injuries to peripheral nerves, showing apparently that the dissociations secured were artefacts dependent on the methods of stimulation employed.

Unfortunately none of these studies of denervation can be considered conclusive, as one or more of the following criticisms can be made of each of them: poor technic; the use of inadequate cutaneous areas; an incomplete presentation of results; an inadequate number of subjects. This unsatisfactory status of the factual basis of generalizations concerning the results of cutaneous denervation suggested the desirability of a repetition of the experiment. It was believed that the apparent contradictions among certain results of previous investigations could be resolved by the use of more than one subject under uniform conditions and by more careful methods of examination and of treat-

2. Trotter, W., and Davies, H. M.: Experimental Studies in the Innervation of the Skin, J. Physiol. **38**:134, 1909.

3. Boring, E. G.: Cutaneous Sensation After Nerve-Division, Quart. J. Exper. Physiol. **10**:1, 1916.

4. Schafer, E. S.: Recovery After Severance of Cutaneous Nerves, Brain **50**:538, 1927; The Effects of Denervation of a Cutaneous Area, Quart. J. Exper. Physiol. **19**:85, 1928; The Permanent Results of Denervation of a Cutaneous Area, Quart. J. Exper. Physiol. **20**:95, 1930.

5. Carr, Harvey: Head's Theory of Cutaneous Sensitivity, Psychol. Rev. **23**: 262, 1916.

6. Cobb, Stanley: Cutaneous Sensibility in Cases of Peripheral Nerve Injury: Epicritic and Protopathic Hypothesis of Head Untenable, Arch. Neurol. & Psychiat. **2**:505 (Nov.) 1919.

ment of results. Accordingly an experiment was planned in which the following principal variations from the procedures in preceding studies were introduced: (1) the use of three subjects simultaneously; (2) a different method of denervation; (3) improvements in the methods of outlining and displaying the zones of anesthesia; (4) more systematic determinations of the thresholds for contact and pain over large areas; (5) careful study of changes in sensitivity.

METHODS OF PROCEDURE

Three phases may be distinguished in the experiment: (1) preliminary work on normal skin for the purposes of standardizing conditions of stimulation, acquiring practice in cutaneous discrimination and establishing norms of sensitivity for the cutaneous areas to be used; (2) denervation operations; (3) study of the effects of denervation and of nerve regeneration on the sensitivity of affected areas. The apparatus and methods used will be described in detail, as indexes of cutaneous sensitivity and outlines of anesthetic areas are peculiarly susceptible to variation with the conditions of stimulation.

1. Preliminary Work.—The volar surface of the left forearm was selected as the general experimental area. Part of this region had been used in each of the four earlier studies of denervation, although only Boring restricted his work to the forearm. This area offers a relatively uniform surface for stimulation, and by means of a plaster cast for each subject's arm it was fairly easy to secure a constant gross position at successive examinations. In order to secure points of reference on the arm and at the same time subdivisions of a considerable area for purposes of stimulation, the cross-section stamp shown as *B* in figure 1 was constructed. The stamp proper is attached to a base which has four legs; by means of springs which connect the base to a frame the stamp can be raised or lowered when the legs are in contact with the skin. After the stamp was placed so that the middle fell half-way between the elbow and wrist, injections of india ink were made at the points on the skin touched by the four legs. These black dots remained as permanent marks, and the stamp could be superimposed readily and with little variation on the experimental area when the arm rested in the plaster cast. The stamped rectangle and the four dots—the sites at which ink was injected—are shown on L's arm in figure 2. The stamp is 50 mm. wide and 70 mm. long; cross-section lines divide its surface into 2 mm. squares. The four heavy lines running longitudinally down the arm in figure 2 represent the courses of the main nerve trunks as outlined by unipolar faradic stimulation.

The apparatus used is shown in figure 1. The instrument labeled *A* is a spring esthesiometer, made from Head's [7] description and used mainly for pain stimulation at constant pressures. A special metal sleeve containing a hair was also devised to fit over the point of the needle, making it possible to use the instrument for light touch stimulation at constant intensities. The steel rod projecting from the cylinder is attached inside to a spiral spring, to which is also fastened the collar shown

7. Head, Henry: Studies in Neurology, New York, Oxford University Press, 1920.

encircling the cylinder. The collar can be moved up or down, thus varying the tension of the spring and consequently the pressure of the stimulus point. The instrument is calibrated in terms of the pressure in grams exerted by the stimulus point when the collar is set at different positions on the scale. The latter runs from 0 to 10 Gm., in steps of 0.25 Gm.

The limen gage, labeled *D*, was made from Boring's specifications [8] and was used in outlining areas anesthetic to light touch stimuli and in measurements of the threshold for both touch and pain. The rod projecting from the metal cylinder was supported by a spring of such tension as to yield pressure varying from 0 to 10 Gm., in steps of 0.25 Gm. Two stimulus points were used: a hair 0.22 mm. in diameter for touch and a needle for pain stimulation. The limen gage and the spring algesimeter, being comparatively heavy and unwieldy, were attached to a segment of curtain spring, as shown in figure 1, and the spring in turn was fastened to a supporting rod. These instruments could then be suspended directly over the subject's arm, and the experimenter, with his arm on a special rest, could bring the point down to the skin easily and steadily.

The von Frey esthesiometer (fig. 1 *E*) was used as an auxiliary touch stimulator. A hair projects from the end of the metal tube. The pressure exerted by the projecting hair depends mainly on its length, and this is varied by sliding the smaller into the larger cylinder. The pressure in grams for a given reading on the millimeter scale can be determined roughly by setting the hair down on a pair of balances.

Dallenbach's thermo-esthesiometer (fig. 1 *F*) was used in punctiform thermal stimulation of the arm. A stream of water of the desired temperature runs in through the outer tubes of the instrument and out through the middle tube. The stimulus point is the tip of a copper wire 1 mm. in diameter and 8 mm. in length, which projects from the cone-shaped temperature chamber. The pressure of the stimulus point on the skin is controlled by a spring inserted between the nonconducting handle and the crosspiece at the top joining the three tubes. The two inlet tubes were connected by rubber tubing with a small galvanized can, which was in turn connected with a large water container. The outlet tube was connected similarly to another can at the same distance from the instrument. Each can contained a thermometer, and the temperature of the stimulating point was assumed to be the mean of the temperature readings of these two thermometers. Water of uniform warmth was secured by means of a heating unit with thermostatic control which was placed in the large container. Cold water of the desired temperature was obtained by running tap water continuously through a copper coil immersed in a mixture of ice, water and salt. By regulating the rate of circulation of the water and by varying the amount of ice about the coil, the desired average temperature could be maintained fairly easily.

The Ebbinghaus double esthesiometer (fig. 1 *C*) was used for two-point stimulation. This instrument makes it possible to regulate both the degree of separation of the points and the pressure exerted by them. The points are conical ebony tips, slightly blunted at the end to avoid producing pain. One of these points was used as the stimulus in the localization tests.

All the preliminary experimental work was done within the stamped rectangle shown in figure 2. Instead of stimulating within each 2 mm. square in the rectangle, nine groups of twenty-five 2 mm. squares were used in all the punctiform examinations. These nine blocks of squares are the numbered areas in figure 2. Measurements of two-point discrimination and of localization were also made

8. Boring,[3] p. 14.

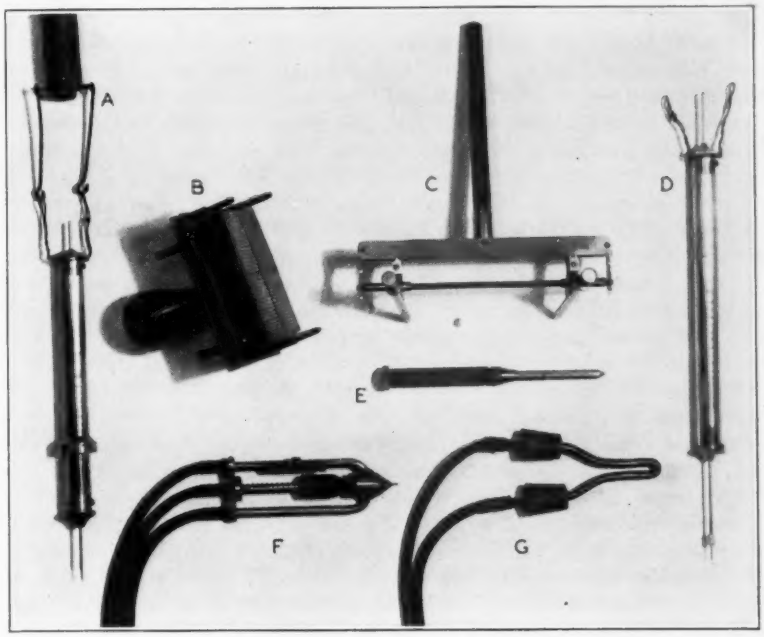

Fig. 1.—Apparatus used in the experiment: *A*, algesimeter; *B*, cross-section stamp; *C*, Ebbinghaus double esthesiometer; *D*, limen gage; *E*, von Frey esthesiometer; *F*, Dallenbach thermo-esthesiometer; *G*, thermal stimulator (used to outline anesthetic areas).

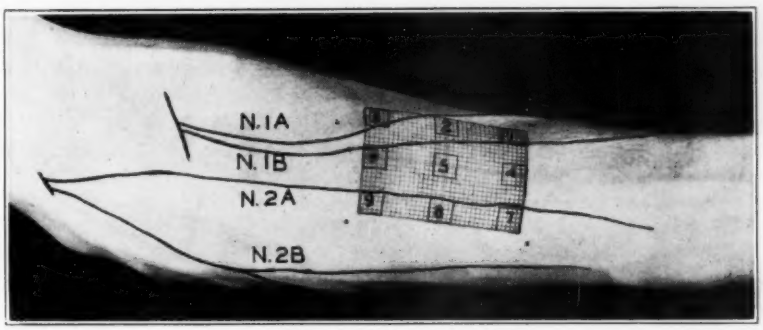

Fig. 2.—Volar aspect of the left forearm of L, showing the stamped area, the nine small squares used in the preliminary work, outlines of the courses of the main nerve branches as determined by faradic stimulation and the points of incision (heavy oblique lines near the elbow). *N.* 1 *A* and *N.* 1 *B* refer to the radial and ulnar branches of the lateral antebrachial cutaneous nerve; *N.* 2 *A* and *N.* 2 *B* refer to analogous branches of the medial antebrachial cutaneous nerve.

within the rectangle. The arm was carefully shaved before any type of experimental work was begun.

The preliminary work was carried out somewhat intermittently over a period of ten months. Once the apparatus was decided on, the principal problems consisted in devising categories of response for each of the types of stimuli and in securing sensitivity indexes from the experimental area with which the postoperative results might be compared. In the case of touch the following categories of response were adopted after much preliminary stimulation and discussion: (1) light touch (a bright, semitickle sensation); (2) pressure (a dull sensation); (3) sharp touch (held by Boring to involve pain). The subject used the numbers 1, 2 and 3 as symbols for these three types of response, respectively; number 4 represented pain from the hair stimulus. In the preliminary series, 675 stimulations were made with the limen gage at each of the following pressures for each subject: 0.25 Gm., 0.5 Gm. and 0.75 Gm. In addition to these stimulations at constant pressures, 210 measurements of the threshold for touch were made with the limen gage. The subject reported the quality of sensation each time, and an experimenter recorded the symbol in a record blank. Results of this preliminary work will be considered later in connection with the measurements of postoperative sensitivity.

A series of pain stimulations, analogous to that of touch stimulations, was made in the same nine blocks of squares. Only two pressures were used, 0.5 and 1 Gm., with 675 stimulations per subject at each pressure. Three intensities of pain were reported by the subject, the numbers 1, 2 and 3 representing mild, medium and acute pain, respectively. Unlike the series for touch, variations in the pain responses could apparently be reduced to differences in intensity. There was a slight tendency toward an increase in intensity of sensation with increase in pressure. A series of 210 measurements of the threshold for pain was made with the limen gage.

The preliminary work on thermal sensitivity involved punctiform stimulation in each 2 mm. square in the nine groups of squares, at six grades of temperature. The temperatures used were 10.5 C., 20.5 C., 27.5 C., 36.5 C., 42.5 C. and 50 C. The numbers 1, 2 and 3 were used to represent mild, intense and extreme warmth or cold, according to the stimulus used; the number 4 was recorded when pain was felt. Three series of trials were made for each subject and for each of the six grades of temperature, making a total of 675 stimulations per subject at each temperature.

All preliminary measurements of localization were made within the stamped rectangle. Two methods were employed: (1) the second method of Weber, in which the subject was asked to touch the point stimulated; (2) a method similar to Henri's, in which the subject was asked simply to name the one of the nine squares in the rectangle which the experimenter had stimulated. In the experiments by the first method the subject sat blindfolded, with the left arm in the plaster cast and the right arm in a predetermined position, holding in the right hand a wooden stylus with a point 1 mm. in diameter. The experimenter applied one of the points of the Ebbinghaus esthesiometer to the intersection of the two axes of the rectangle, and the subject tried to place the stylus on the exact point stimulated. He was allowed to move the point about on the skin until he was satisfied with the localization. Three intensities of stimulus pressure were used: 2, 7.5 and 15 Gm.; 40, 80 and 40 trials, respectively, were made at these three grades of pressure. The subject's error in localization was recorded each time in terms of distance from each axis.

The second method of measuring accuracy in localization required that the subject name the one of the nine large experimental squares stimulated. The

experimenter touched the center of a square with the point of the Ebbinghaus esthesiometer, and the subject, who was blindfolded, called out the number of the square in which he localized the stimulus. In this experiment again three degrees of pressure were used: 2, 5 and 15 Gm. Twenty trials were made, in random order, for each square, at each pressure, or a total of 540 localizations for each subject.

The Ebbinghaus double esthesiometer was used for two-point stimulation. The subject sat blindfolded, with his arm in the cast, while the experimenter pressed the points down on the skin simultaneously and removed them. Two points were always used, and the subject was instructed to report "one" in all cases in which two points were not definitely perceived.

The longitudinal and transverse axes of the rectangle were the lines along which two-point discrimination was measured. Preliminary experimentation served to establish roughly the limits within which the limen was expected to lie. Then seven degrees of separation, differing by equal (4 mm.) increments were chosen for the experimental series. The same seven separations were used for all three intensities of pressure. Twenty stimulations per subject at each of the seven separations constituted a complete series for a given pressure. This gave a total of 140 judgments for the computation of each limen, i. e., 140 judgments for each subject at each of the three grades of pressure. These cases are, of course, too few to rule out all variability and inconsistency in the percentage of "two" judgments for each stimulus separation and to justify the use of the more elaborate methods of computing the limen based on fitting a smooth curve to the data. As the lowest and highest separations of the points for each subject were sufficient to give in the majority of instances percentages of 0 and 100 for the "two" judgments, respectively, the arithmetical mean method of Spearman was used to compute the limens.

2. Operation.—The volar surface of the left forearm is innervated mainly by two nerves, each of which emerges from the deep fascia near the elbow and divides into two branches. The courses of the principal branches of each nerve, as determined by unipolar faradic stimulation, are indicated by the heavy solid lines in figure 2. The two divisions of the lateral antebrachial cutaneous nerve are labeled *N.* 1*A* and *N.* 1*B* (radial and ulnar divisions), while the radial and ulnar branches of the medial antebrachial cutaneous nerve were called *N.* 2*A* and *N.* 2*B*, respectively. It was not considered essential to block identical nerve branches in all three subjects, as great individual differences in overlapping and distribution exist. The important problem was to secure in all three subjects areas of sufficient extent to insure complete cutaneous denervation.

Two series of operations were performed. In the first series each subject received one injection of alcohol into one nerve branch. After approximately three weeks, during which careful exploration had revealed the limited extent of the anesthesia, a second series of operations was performed, in which injections were made into additional nerve branches. Table 1 contains a summary of the nerves involved and the dates of the injections for each subject.

The general procedure was the same in all the operations. The skin was infiltrated with procaine hydrochloride and an incision made near the elbow, where the nerve branch had been located by faradic stimulation. When the nerve was exposed it was stimulated by being lightly clamped with a hemostat; peripheral reference of the effects of such stimulation enabled the subject to localize the approximate area to which it was distributed. Then procaine hydrochloride was injected into the nerve, and the skin stimulated with a needle to determine roughly the extent of anesthesia. Finally, alcohol in 95 per cent concentration was injected into the nerve and the incision closed up. All the incisions healed rapidly.

3. Methods of Studying the Effects of Denervation and Nerve Regeneration.—The study of changes in sensitivity produced by the denervation of a cutaneous area naturally required experimental procedures different from those used in the preliminary work on normal skin. The special problems involved may be stated as follows: (1) the study of the interrelations of the several modes of sensibility as indicated by possible spatial or temporal dissociations; (2) the measurement of possible gradations in sensitivity in zones intermediate between normal and anesthetic skin; (3) the study of changes in quality or intensity of sensation in affected areas; (4) comparisons of normal, hypesthetic and anesthetic skin with respect to two-point discriminability; (5) similar comparisons as regards ability to localize stimuli. The specific methods used in the measurements of two-point discrimination and of localization did not differ from those already described for normal skin, except that only one grade of pressure (15 Gm.) was employed. The requirements of the first three problems, however, necessitated special modifications of procedures, the general nature of which will now be briefly described.

(a) Methods of Mapping Anesthetic Areas: Perhaps the most distinctive feature of the present study is the method of outlining and portraying the zones of anesthesia to the four types of cutaneous stimuli. In view of conflicting reports

TABLE 1.—*Summary of Nerves Into Which Injections Were Made and Dates of Operations for Each Subject* *

Subject	First Operation		Second Operation		Both Operations
	Date	Nerve	Date	Nerve	Nerve
C.....	7/2/31	N.2A	7/24/31	N.1A	N.1A, N.2A
L.....	7/6/31	N.1A	7/29/31	N.1B, N.2B	N.1A, N.1B, N.2B
W.....	7/2/31	N.2A	7/24/31	N.1A, N.1B	N.1A, N.1B, N.2A

* The symbols for the nerves are as follows: N.1A and N.1B indicate the radial and ulnar branches of the lateral antebrachial cutaneous nerve, and N.2A and N.2B, the radial and ulnar branches of the medial antebrachial cutaneous nerve (fig. 2).

of previous investigators regarding the patterns of dissociation observed, it was considered especially necessary to employ careful methods of mapping zones of sensory loss. The constant intensity of stimulus used for each of the four types of sensitivity was selected after considerable testing had shown that higher intensities used in the manner to be described did not yield systematically smaller anesthetic areas. The procedure for touch will first be described and, more briefly, that for pain, cold and warmth stimuli.

The arm was carefully shaved before each mapping. The subject sat with closed eyes while the experimenter began stimulating with the limen gage hair tip, well within the anesthetic area. A pressure of 1 Gm. was used throughout. Stimulating at a rate of about one contact per second on points about 1 mm. apart, the experimenter worked outward toward normal skin. The subject responded when he first felt the contact, and the experimenter made a dot with ink on the skin at that point. Then the procedure was repeated, beginning at a point about 5 mm. from the site of the first trial. This procedure was continued until the entire area was outlined. Several points in the outline were then rechecked to determine the reliability of the original mapping. This method of rapid punctiform stimulation at constant pressure was considered a great improvement over the rough outlining with cotton-wool or a camel's hair brush, the stimuli used by

earlier investigators.[9] Our outlines were checked on several occasions by mapping with a camel's hair brush, and the punctiform method usually gave a much smaller anesthetic area.

The area for pain was outlined in a similar manner, with the use of the algesimeter at a pressure of 4 Gm. Ink of a different color was used to mark the boundary line for pain. This method of stimulating points close together in fairly rapid succession, while constituting punctiform stimulation, nevertheless may be considered a rough approximation to areal stimulation. It tends to combine the advantages of both methods and yielded narrower anesthetic areas than did heavier pressures applied slowly, as in the measurement of thresholds.

The areas of cold and warmth anesthesia could not be readily outlined by the punctiform method, owing to the relative scarcity of the spots for warmth and cold on the skin. Accordingly a special thermal stimulator was constructed with which these outlines could be easily made. The instrument (fig. 1 *G*) consists simply of a copper tube 3 mm. in diameter, bent to form a Y. The two arms of the Y are the inlet and outlet tubes through which water flowed from the temperature control sources already described. A cork was fitted over each arm to avoid contact of the experimenter's hand with the metal. The rounded end of the tube provided a smooth stimulating surface. By passing this stimulator from the center of the anesthetic region slowly outward toward normal skin it was comparatively easy to outline the zones of anesthesia to cold and warmth stimuli.

When the four mappings were completed the dots made by ink of different colors were replaced by the following types of outlines, drawn in india ink: for light touch, a broken line; for pain, small dots; for cold, a solid line; for warmth, large dots. The subject then placed his arm in the plaster cast, and an impression of the rectangular stamp was made on the arm, to serve as a landmark. The arm was then photographed. After the second operation two views of the arm of C and W and three views of the arm of L were necessary to show all the areas affected.

These mappings and photographs were made weekly for all the subjects during the first ten weeks following the first operation. The weekly schedule was continued for L until nineteen weeks after the first operation and thereafter at intervals of two weeks until all the functions were restored; for C and W the mappings were made approximately every two weeks from the tenth week until the twenty-third week. Thereafter the mappings for these subjects were made less frequently. The total number of mappings for each subject was twenty-seven, although differences in the rates of the return of sensitivity resulted in relatively more frequent outlining for L than for the other two subjects.

(b) Measurement of Thresholds for Contact and Pain: The sizes of the affected areas in all three subjects prevented the measurement of thresholds on all of the cutaneous surface involved. It was necessary to select representative regions and to restrict the determinations of the threshold largely to these areas throughout the course of the work. In general, the plan adopted was to use cross-sections of skin at different levels of the subject's arm, each section extending from approximately normal skin on the radial side across the affected zones to normal skin

9. In the course of the first two mappings after the first operation an outline was made of the areas which felt abnormal to the subject. This was done by having the subject stroke the skin with his right forefinger. As this method did not appear to be reliable, the outline for stroking was discontinued. This outline appears as the heavier solid line in the photographs shown for each subject after the first operation.

on the ulnar side. In the case of L, the cross-sections ran across the arm and well into the anesthetic area of the ulnar portion of the arm; the section could not be extended onto normal skin on the ulnar side in this case owing to the difficulty which would have been encountered in getting the arm into a position suitable for stimulation. Each cross-section was 4 mm. in width, and consisted of two rows of the 2 mm. squares which were stamped on the arm. The levels of the arm used throughout the study on all three subjects were: (1) the upper two proximal rows of the stamped rectangle, and (2) the fourth and fifth rows from the lower, or distal, end of the rectangle. In order to cover the entire lateral extent of the intermediate and anesthetic zones it was necessary to stamp additional 2 mm. squares on each side of the rectangle. In addition to these two regularly used 4 mm. cross-sections, others were studied from time to time for the purpose of measuring the sensitivity of special areas or of checking the results on the regular segments.

The thresholds were measured with the limen gage, the tip of the hair being used for contact stimulation and the point of the needle for pain. The subject was blindfolded, and the experimenter touched the center of one of the 2 mm. squares, gradually increasing the pressure until the subject responded. The intensity (or quality) of the sensation, in terms of symbols described for the preliminary work, was entered on the record blank, together with the pressure reading of the limen gage. (Special symbols were introduced to indicate the peculiar protopathic qualities of sensation frequently felt). These limens for touch and pain were measured weekly for all subjects during the first seven weeks following the second operation. Thereafter the measurements were made for C and W approximately every two weeks until the experiments were discontinued. The regular limen measurements for L were made more frequently, and, in addition, many special series were run. Approximately 13,000 determinations of the threshold for touch and 15,500 determinations of the threshold for pain were made on L; 6,370 determinations of each on C, and 5,855 of each on W.

(c) Qualitative Changes in Sensitivity: Data concerning the nature of alterations in the character of sensation were secured mainly in connection with the determination of the thresholds, in the form of estimates by the subject of the intensity (for pain) or of the quality (for contact) of the sensations produced. Analogous symbols for sensations produced by stimulating normal skin have already been described. Soon after the operations the protopathic pain described by other investigators was observed in the intermediate zone. Thereafter whenever this itching, extremely unpleasant response occurred, the symbol for intensity was encircled. If the response was referred (all reference was peripheral), an additional symbol indicated this fact. In addition to the records secured during the systematic determination of the thresholds, reports of the character of the sensations from incidental contact, from stroking and from the stimulation occurring during the mappings were included in the diaries. Furthermore, in the case of L, numerous special measurements of the thresholds for touch and pain and special punctiform tests of sensitivity to cold were made in which estimates of the intensity or quality of sensation were recorded.

SENSORY DISSOCIATIONS BEFORE AND DURING NERVE REGENERATION

The types of dissociations observed are shown in a series of outlines for each of the five experimental areas. Figures 3 and 4 contain the series for the affected region on the radial side of L's arm. Corresponding photographs of two views of the area affected by injection into the

ulnar branch of the medial antebranchial cutaneous nerve are shown in figures 5 and 6. Photographs of the ulnar and radial views, respectively, of C's arm are shown in figures 7 and 8; analogous photographs for W are presented in figures 9 and 10.

Figure 3*A* shows the regions of anesthesia on the thirteenth day after the first injection into the nerve of L's arm (*N.* 1*A*). The heavy outline for stroking, discarded after this date, reveals that a considerable portion of the skin outside any of the anesthetic boundaries felt abnormal. The outlines for cold and warmth lie far outside those for touch and pain and tend to conform fairly closely, except in the distal end of the region. (In the mappings for the preceding and the following weeks, not shown here, the outline for cold anesthesia extended much further in the peripheral direction and hence approximated much more closely that for warmth anesthesia than is the case in figure 3*A*). The regions anesthetic to light touch and those anesthetic to pain stimuli coincide in part, although an area sensitive to touch but insensitive to pain stimuli is shown along the ulnar border of the region. This area was carefully checked and seemed to correspond to Head's triangle in which epicritic sensitivity was present, dissociated from protopathic sensitivity. No thermal sensitivity was present within this small zone, as the outlines indicate.[10]

The status of sensibility in the same region after the second operation is shown in figure 3*B*. The pattern of the sensory dissociations displayed here agrees in general with that shown in figure 3*A*. Although the extent of anesthesia to cold, is occasionally less than that to warmth stimuli, both these outlines lie far outside the zones of anesthesia to touch and pain. This greater loss of thermal sensitivity as compared with the loss of touch or pain sensitivity, could scarcely have been due to differences in the methods of stimulation, since the use of the larger areal thermal stimuli should have reduced rather than increased the size of the areas displayed as anesthetic. Furthermore, the border of the area of sensitivity to cold stimuli, especially, was so definite and easily located that the greater loss discovered for this function could scarcely have been an artefact.

Comparisons of the outlines for sensitivity to touch and pain stimuli in figure 3*B* show unusually good conformity except along the lower radial side of the rectangle. A large triangular area there was sensitive to touch stimuli at a pressure of 1 Gm. but entirely insensitive to pain stimuli at a pressure of 4 Gm. (even greater pressures failed to elicit pain anywhere in this area). This zone was an extension of the narrow band shown in figure 3*A*, and it possessed the sensory properties of Head's triangle, except that no thermal response could be elicited in our area. These results agree with the observations made by Trotter and Davies [11] on a similar area.

The status of sensibility on the forty-second day after the first operation, and the nineteenth day after the second, respectively, is shown in figure 3*C*. The outlines do not differ markedly from those in figure 3*B*. There is the same type of conformity in the outlines for warmth and cold sensitivity and, with the exception of the triangle, in those for touch and pain sensitivity. The outline for cold sensitivity is slightly shorter just distal to the scar, although it is doubtful whether this is due to nerve degeneration. It is more likely, in view of the fact that a few spots sensitive to warmth stimuli were found there also, that the

10. The black dot about 1 cm. centrad to the upper border of the rectangle is a mole, not a spot for warmth, as might be inferred from its appearance in the photograph.

11. Trotter and Davies,[2] p. 214.

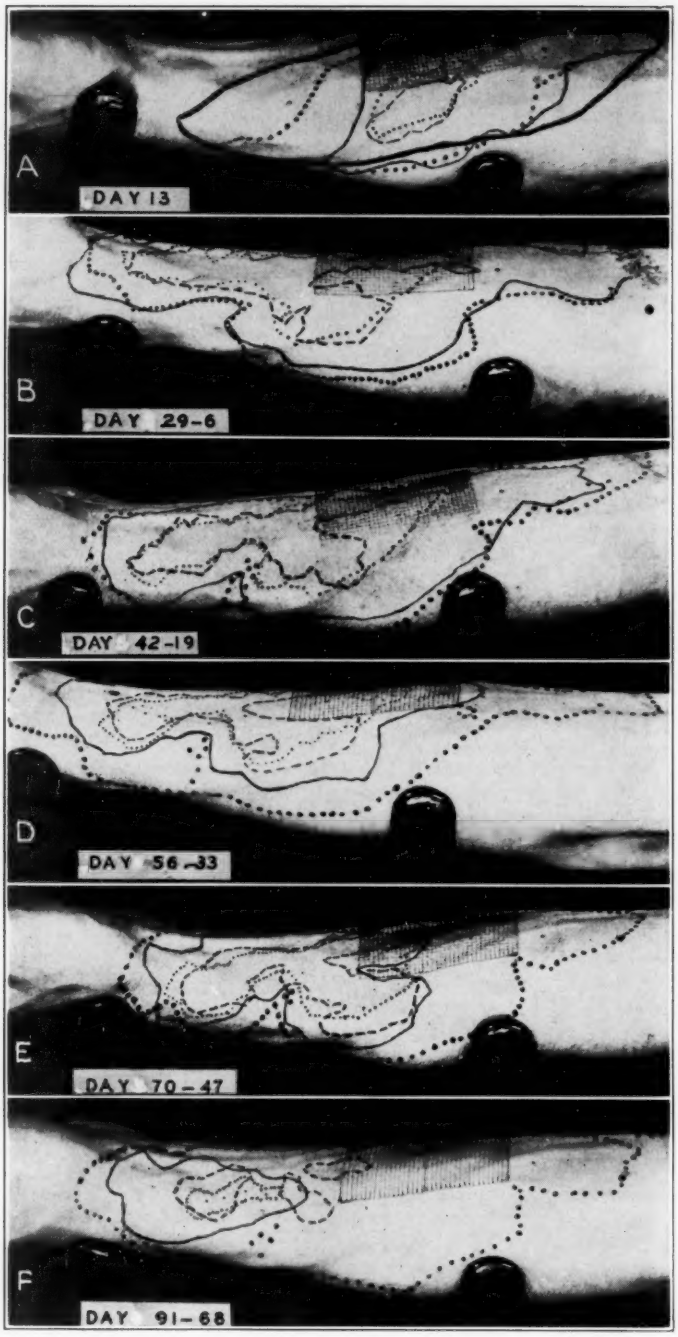

Fig. 3.—Record of observations on L. *A*, outlines of anesthetic areas after the injection of alcohol into the radial branch of the lateral antebrachial cutaneous nerve (first operation). In all the views of the arm in this and subsequent figures the four types of anesthesia are represented as follows: pain, small dots; contact, broken line; cold, thin solid line, and warmth, large dots. The outline for stroking is represented by the heavy solid line. *B* to *F* show outlines of anesthetic areas and the order of return of sensation after injection into the ulnar branch of the lateral antebrachial cutaneous nerve (second operation). The outline for stroking was omitted after the second operation. In this figure and in figure 4 the days are counted from the day of the first and from that of the second operation, respectively.

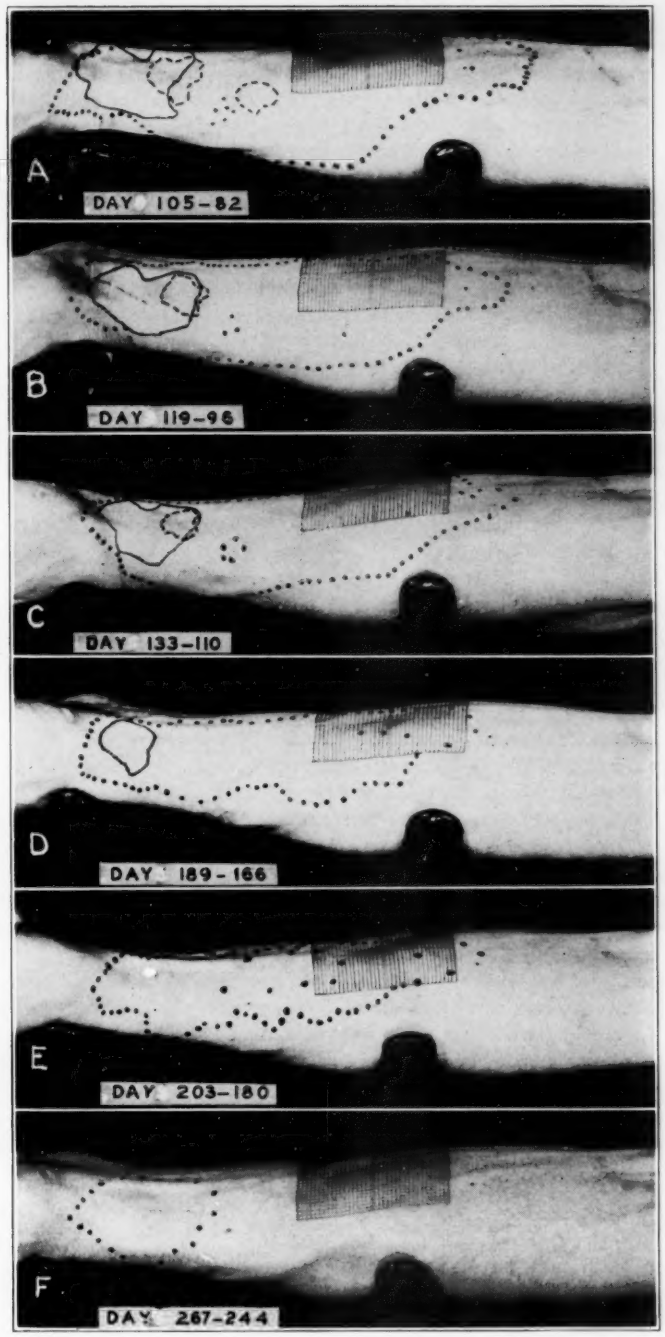

Fig. 4.—Continuation of the series of mappings on L's arm, showing return of sensation in the portion of the arm innervated by the radial and ulnar branches of the lateral antebrachial cutaneous nerve.

mapping a week after the operation was not representative of the status of innervation near the incision, owing to the abnormal condition of the skin so soon after the operation. The greatest discrepancy noted, in comparison with the findings recorded in the preceding photograph, is the apparent reduction in the extent of the zone of anesthesia to touch stimuli on the upper radial corner of the triangle. However, the outlines for sensitivity to touch stimuli for both the preceding and the succeeding weeks approximated fairly closely at that point the outline shown in figure 3 *B*. As no sharp line of demarcation between anesthetic and normal skin exists, such functional variations in efficiency in hypesthetic skin are to be expected.

The first definite evidence of return of sensation due to nerve regeneration was noted in the outlines for the forty-ninth day after the first operation and the twenty-sixth day after the second (the photograph is not shown). There were a definite recession of the outline of anesthesia to cold in the region proximal to the scar and a similar slight shortening (from 8 to 10 mm.) of the outlines for pain and touch. In figure 3 *D*, showing the outlines on the fifty-sixth day after the first operation and the thirty-third day after the second, there is a decided decrease in the areas anesthetic to cold, pain and touch stimuli. No change in warmth sensitivity is noted. The course of return of the four modes of sensibility over this area is shown clearly in figures 3 *E* and *F* and 4 *A* to *F*. In general, sensitivity to pain, touch and cold stimuli tended to return at about the same rate, with a slight tendency to the order of precedence in which the sensations are listed. Sensitivity to warmth stimuli returned much more slowly.

The results of the outlining of the second anesthetic area of L are shown in figures 5 and 6. This enormous anesthetic zone was produced by injection into only one branch (the ulnar) of the medial antebrachial cutaneous nerve. As this nerve branch appeared no larger than the radial branch of the lateral antebrachial cutaneous nerve it seems probable that innervation on this protected side of the arm was less adequate than on the more exposed radial side. These facts are interesting from a general biologic point of view, indicating a correlation between complexity of innervation and susceptibility to stimulation.

It was necessary to photograph the arm in two positions in order to display the extent of anesthesia produced by blocking the ulnar branch of the medial antebrachial cutaneous nerve in L. The first position is that shown in figure 5; the second is that shown in figure 6. The two figures contain six photographs each for corresponding views of the arm on the sixth, twenty-sixth, forty-seventh, sixty-eighth, one hundred and third and one hundred and sixty-sixth day after the operation (this area was affected only by the second operation). The first photographs (figs. 5 *A* and 6 *A*, taken on the sixth day) show that generally the outlines for anesthesia to touch and pain stimuli conform closely and tend to lie considerably within those of anesthesia to cold and warmth stimuli. There is no decided dissociation of sensitivity to touch from that to pain stimuli such as was discovered in the case of the triangle in the radial area. These two outlines intermingle irregularly. The same general observations hold for the outlines of sensitivity to cold and warmth stimuli, although there is by no means perfect coincidence. There is an area in the proximal region in figure 6 *A* which was apparently anesthetic to cold stimuli but sensitive to warmth stimuli. Subsequently weekly mappings did not confirm this result, however, and it may be considered merely accidental.

Figures 5 *B* and 6 *B* (twenty-sixth day) display an exceptional conformity of the outlines for sensitivity to touch and to pain stimuli, while the agreement between the outlines for sensitivity to cold and warmth stimuli is only slightly less good.

The areas of thermanesthesia are considerably greater than those of anesthesia to touch and to pain stimuli. In view of the relative scarcity of cold and warmth spots on the normal skin, it is perhaps surprising that the agreement in the outline of anesthesia to warmth and cold stimuli is so good. The reliability of these results is attested by the fact that the mappings for the two weeks preceding and the week following this mapping agreed well with the latter.

The outlines for sensibility to pain and touch stimuli for the forty-seventh day (figs. 5*C* and 6*C*) indicate that a slight diminution had occurred in the extent of anesthesia in the proximal region. Otherwise the status of sensibility in the area remained practically the same as in the mappings made three weeks earlier. The general order of return of sensation is shown in the remaining figures in these series (figs. 5*D* to *F* and 6*D* to *F*). Sensitivity to pain, cold and touch stimuli returned at about the same rate, with a slight tendency to that order of precedence. Sensitivity to warmth stimuli was greatly delayed, returning to the extreme distal region about three months after the final photographs shown were taken. In general, the results agree well with those for the other area.

The effects of injections into the radial branch of the medical antebrachial cutaneous nerve (*N. 2A*) in C are illustrated in figure 7*A*. The loss of thermal sensibility is considerably greater than the loss of touch or pain sensitivity, especially in the distal region. Pain anesthesia is somewhat less than that to touch, although along the ulnar border the outlines for these two classes of stimuli are almost identical.

In the second operation, performed twenty-two days after the first, injections were made into the radial branch of the lateral antebrachial cutaneous nerve. This produced a second anesthetic area separated from the first by skin for which the primary nerve supply remained intact. The status of sensibility after the second operation is indicated by the outlines in figures 7*B* and 8*A*, which display ulnar and radial views of the arm for the forty-sixth and twenty-fourth day (the date from the day of the first operation is given in the ulnar views, and that from the day of the second in the radial views). The outlines for touch and pain sensitivity manifest unusually good conformity, as do those for warmth and cold sensitivity. The loss of thermal sensitivity is considerably greater than that of touch or pain sensitivity, and this agrees with the results on the two areas on the arm of L.

There are, however, several striking anomalies in the distribution of sensitivity on this arm. Perhaps the most remarkable is the complete absence of thermal sensitivity over the area supplied by the intact nerve which runs between the two anesthetic zones. It can be seen from figure 7*B* that a small wedgelike area just distal to the elbow is the only place which retains sensitivity to warmth and cold, although sensitivity to touch and pain are apparently normal on a broad band of skin which extends down the center of the arm, far below the distal border of the stamp. This presents a peculiar and interesting neurologic problem, one which is undoubtedly related to the phenomenon already noted of a more extensive loss of sensitivity to thermal stimuli than of the loss of touch or pain sensibility.

Other peculiarities in the distribution of anesthesia were the extensive proximal loss of cold and warmth sensitivity, the small proximal patch insensitive to touch or pain stimuli and the broad band of anesthesia extending entirely across the arm near the wrist. The first two phenomena can perhaps be attributed to interruption of small local nerve branches during the extensive exploration for the second branch of the lateral antebrachial cutaneous nerve at the second operation. The interesting point about these two phenomena is that the pattern of the dissociations agrees with that already observed.

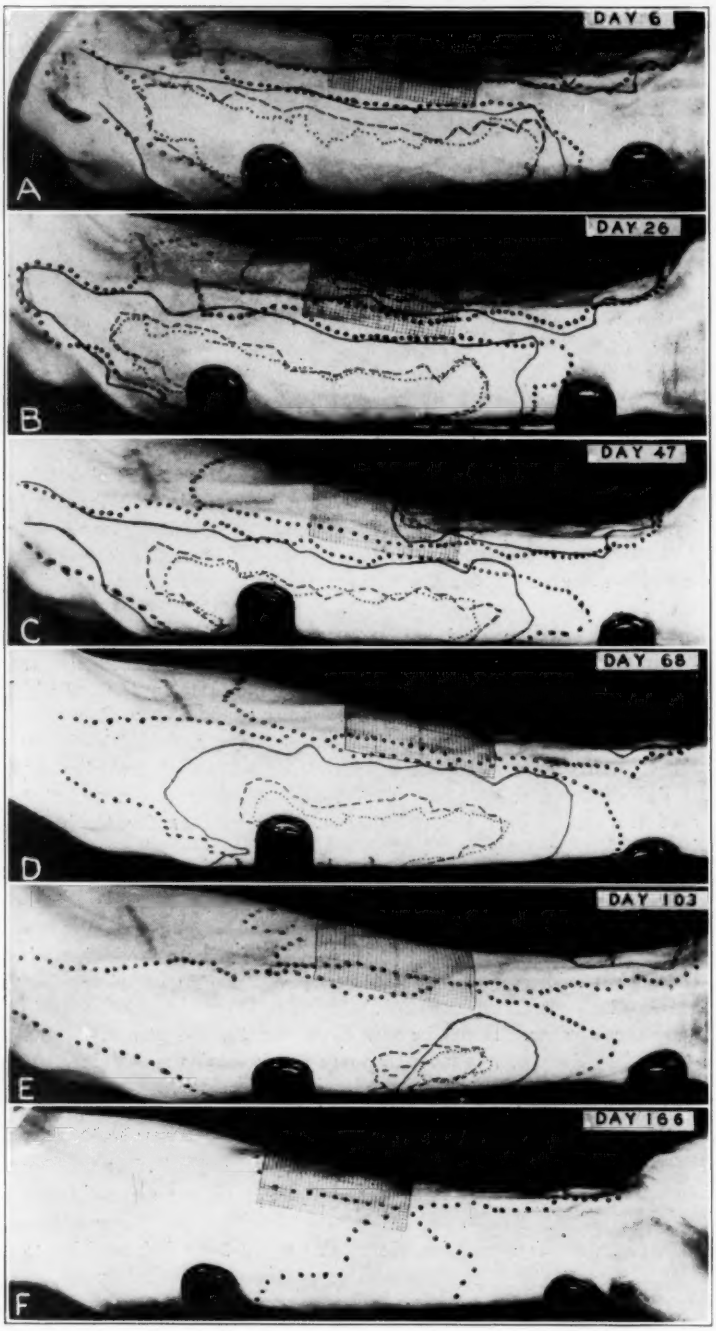

Fig. 5.—Observations on L. Outlines of anesthetic areas and of areas showing return of sensation in the portion of the arm innervated by the ulnar division of the medial antebrachial cutaneous nerve. The upper part of the area is shown in figure 6. The days are counted from the day of the second operation.

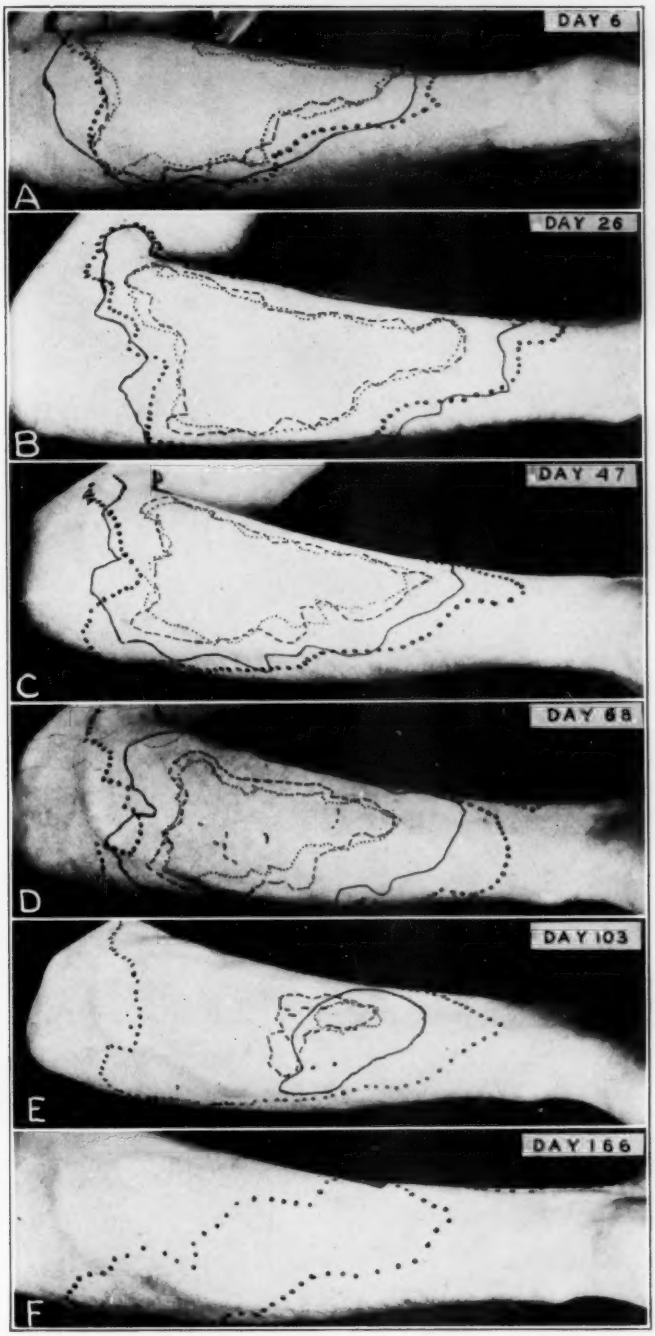

Fig. 6.—Observations on L. Second view of the portion of the arm innervated by the ulnar division of the medial antebrachial cutaneous nerve, showing outlines of anesthetic areas and the order of return of sensation. The isolated area innervated by the radial division of the medial antebrachial cutaneous nerve is shown along the ulnar border of the rectangle; no injection was made into the nerve supplying this area.

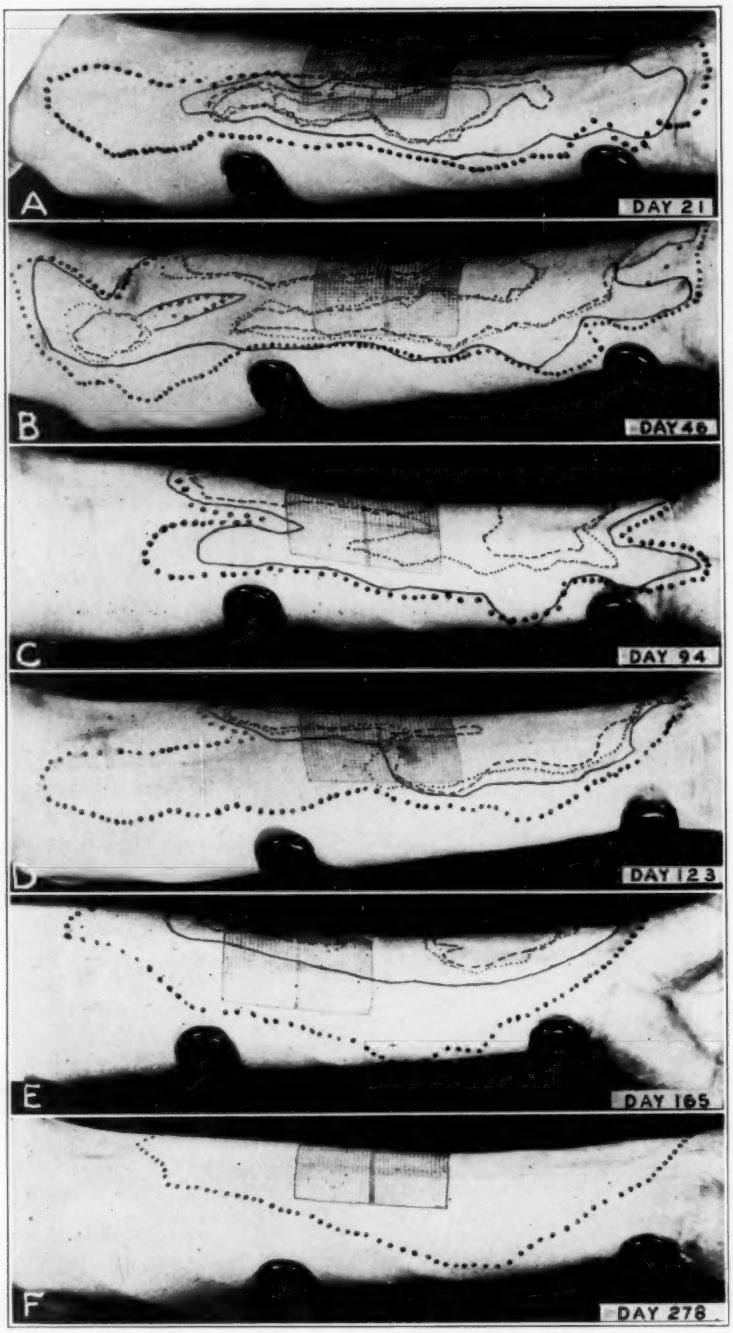

Fig. 7.—Observations on C. *A*, outlines of anesthetic areas after injection into the radial division of the medial antebrachial cutaneous nerve (first operation). *B* to *F*, outlines of areas showing return of sensation in the portion of the arm innervated by the radial division of the medial antebrachial cutaneous nerve. The anesthesia on the radial side of the arm was produced by injecting alcohol into the radial division of the lateral antebrachial cutaneous nerve at the second operation. The isolated area innervated by the ulnar division of the lateral antebrachial cutaneous nerve, separating the two anesthetic areas, is shown clearly along the middle of the rectangle. The days are counted from the day of the first operation; the second operation was performed twenty-two days later.

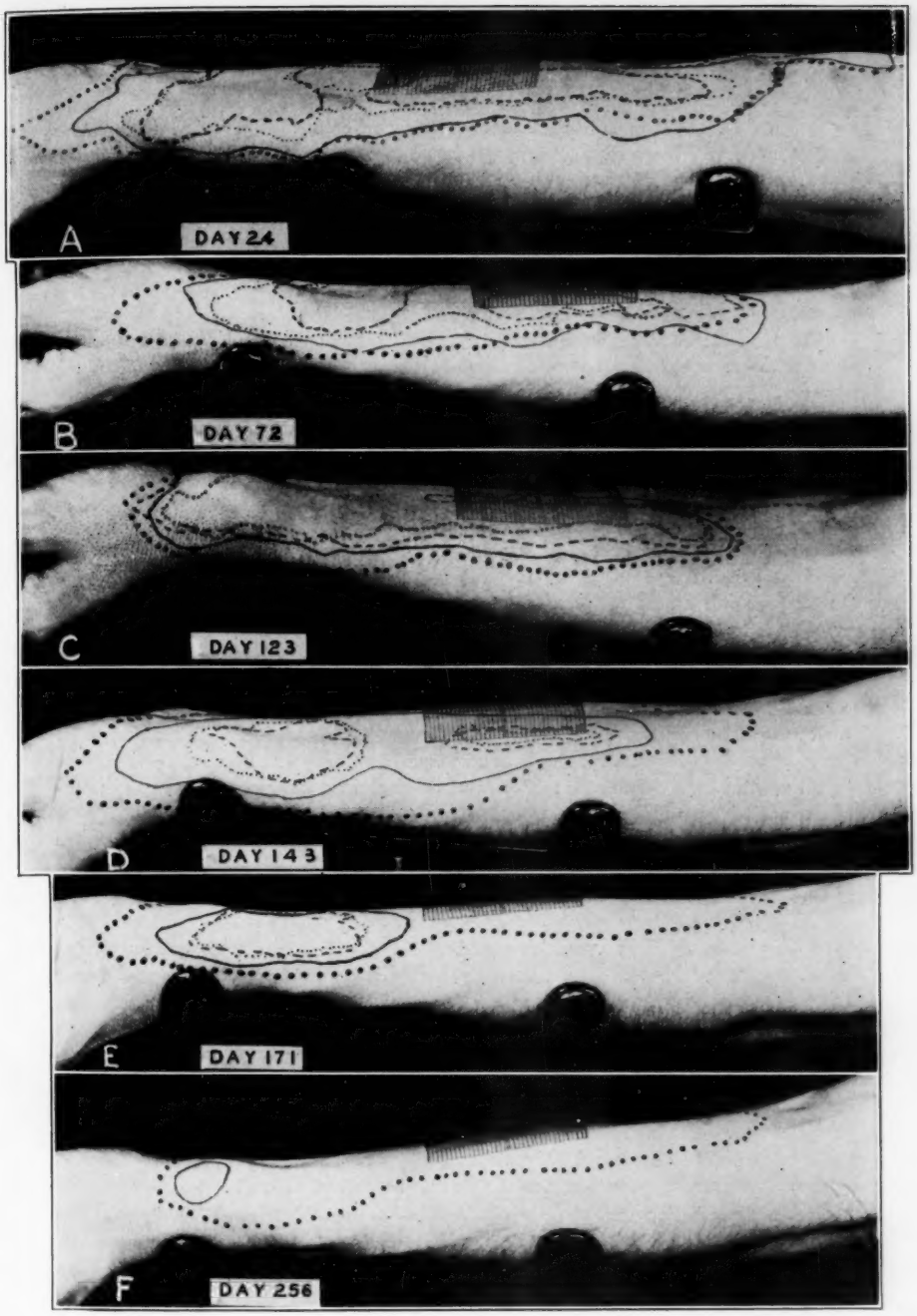

Fig. 8.—Observations on C. Outlines of anesthetic areas and of areas showing return of sensation in the portion of the arm innervated by the radial division of the lateral antebrachial cutaneous nerve. The days are counted from the day of the second operation.

The course of return of sensation to the ulnar zone is illustrated in figures 7 *C* to *F*. Anesthesia to touch seems to diminish more rapidly at first than that for pain or cold, although figure 7 *D*, a photograph taken four weeks after that shown in figure 7 *C*, contradicts the results of the earlier mapping. The intervening photographs, which are not shown, confirm the outlines in the later photograph. Such an anomalous fluctuation indicates the variability encountered in the sensibility of recovering areas. The general order of return appears to agree with that found for L, sensitivity to touch, pain and cold stimuli returning at about the same time and rate, and great delay being evident in the restoration of warmth sensitivity. The results shown for the radial area conform to this general formulation, as inspection of figures 8 *B* to *F* shows.

The first injection into the radial branch of the medial antebrachial cutaneous nerve in W resulted in denervation of a small area on the lower ulnar half of the forearm. The outlines of anesthesia, as nearly as they could be determined on the twenty-first day, are shown in figure 9 *A*. There was such fluctuation in these outlines in successive mappings, however, that little reliance can be placed on them. When injections were made into the radial and ulnar branches of the lateral antebrachial cutaneous nerve in the second operation, an enormous anesthetic zone was produced, extending from slightly above the elbow to the wrist. The ulnar view of the area is shown in figure 9 *B* and the radial view in figure 10 *A* (the day in the ulnar series is computed from the day of the first operation, while that in the radial series is counted from that of the second). The outlines for pain and touch virtually coincide, with the exception of a small zone near the wrist on the radial side, which was sensitive to touch but not to pain stimuli. Anesthesia to warmth is much more extensive than that to touch or pain stimuli. The outline for sensitivity to cold stimuli is usually intermediate between the outlines for sensitivity to warmth, and those for sensitivity to touch and pain stimuli, although on the radial side it tends to coincide with the boundary for warmth. The area of anesthesia to warmth stimuli was much more difficult to outline, sensibility to this type of stimulation being hypesthetic and instable in the intermediate zone.

The zones of touch and pain anesthesia, especially the latter, manifested considerable lateral shrinking on W's arm, presumably before any nerve regeneration began. A comparison of figure 10 *B* (the hundred and seventh day after the first operation and the seventy-ninth day after the second) with figures 9 *B* (the forty-sixth day after the first operation) and 10 *A* (the twenty-fourth day after the second operation) reveals that whereas none of the outlines had shortened much in the proximal-distal direction, the analgesic zone was greatly reduced in lateral extent. It should be noted that neither in the mappings made before nor in those made after the one shown in figure 10 *B* was the outline for pain sensitivity so narrow within the region of the rectangle. The cause of the spotty pain sensitivity reported on that day is unknown. It should be noted, however, that these boundaries are not fixed; anomalous functional variations in the efficiency of the residual fibers of the intermediate zone would have been expected. W showed more variable reactions throughout the experiment than C or L.

Nerve regeneration was greatly delayed in W in comparison with that in the other subjects. No distal shortening which might reasonably be attributed to regeneration was observed before the hundred and twenty-third day after the first operation and the hundred and first day after the second (in contrast with the forty-ninth day after the first operation and the twenty-sixth day after the second for L and the sixty-first day after the first operation and the forty-ninth day after the second for C). Even after this apparent beginning little or no further change

was recorded for six weeks. After that, as figures 9 *D* to *F* and 10 *D* to *F* show, sensitivity to pain, touch and cold stimuli began to return slowly and approximately together. As in the other subjects, the return of warmth sensitivity occurred considerably later than sensitivity to pain, touch and cold stimuli.

A striking anomaly in the course of recovery in W was the failure of sensitivity to touch and pain stimuli to return to a small patch of skin in the midproximal region of the rectangle. A small region there was still anesthetic to both forms of stimuli a year after the final photograph shown was taken.

THRESHOLDS FOR TOUCH AND PAIN

In the preceding section the interrelations of the several types of cutaneous sensation, as revealed by appropriate forms of stimulation at constant intensities, were considered. Such a technic could not reveal possible gradations in sensitivity in intermediate zones and in recovering areas. Accordingly, a quantitative study of thresholds for touch and pain was instituted to complement the results secured with stimuli of constant intensities. These measurements constitute indexes of the functional efficiency of the neural mechanisms operative in the various areas studied.

The results of the measurements of the thresholds are presented in two forms: (1) a series of charts showing individual limens secured in the 2 mm. squares of the cross-sections of skin selected for study (figs. 11 to 17); (2) tables summarizing the data on these limens for typical intermediate and recovering areas (tables 2, 3 and 4). Each of the charts contains values for the thresholds determined on two representative segments of skin for each subject. In order to facilitate the comparison of the thresholds for touch and pain, the charts for these functions, based on data secured on corresponding days, are placed on opposite pages. Thus, figure 11 shows the limens for touch, while figure 12 shows the corresponding limens for pain; similarly placed on opposite pages are figures 13 and 14, and figures 15 and 16; in the chart on the last page of the series (fig. 17) *A* and *B* show thresholds for touch, while *C* and *D* show thresholds for pain.

An explanation of L's record in figure 11 *A* will facilitate the interpretation of these charts for the thresholds. The small squares in the figure represent the original 2 mm. squares which were stamped on the arm. Stimulation with the tip of hair of the limen gage in each of these squares elicited either a response within the limits of the pressure indicated or no response up to the maximum pressure of 5 Gm. The blank squares represent the latter cases. With reference to the location of the cross-sections on the arm, the upper cross-section in every case runs across the proximal end of the stamped rectangle, from the ulnar to the radial side of the arm; the lower cross-section runs in the same direction across the arm and includes the fourth and fifth rows of squares from the distal end of the rectangle. The left (ulnar) side of both cross-sections represents the anesthetic area innervated by the ulnar branch of the medial antebrachial cutaneous

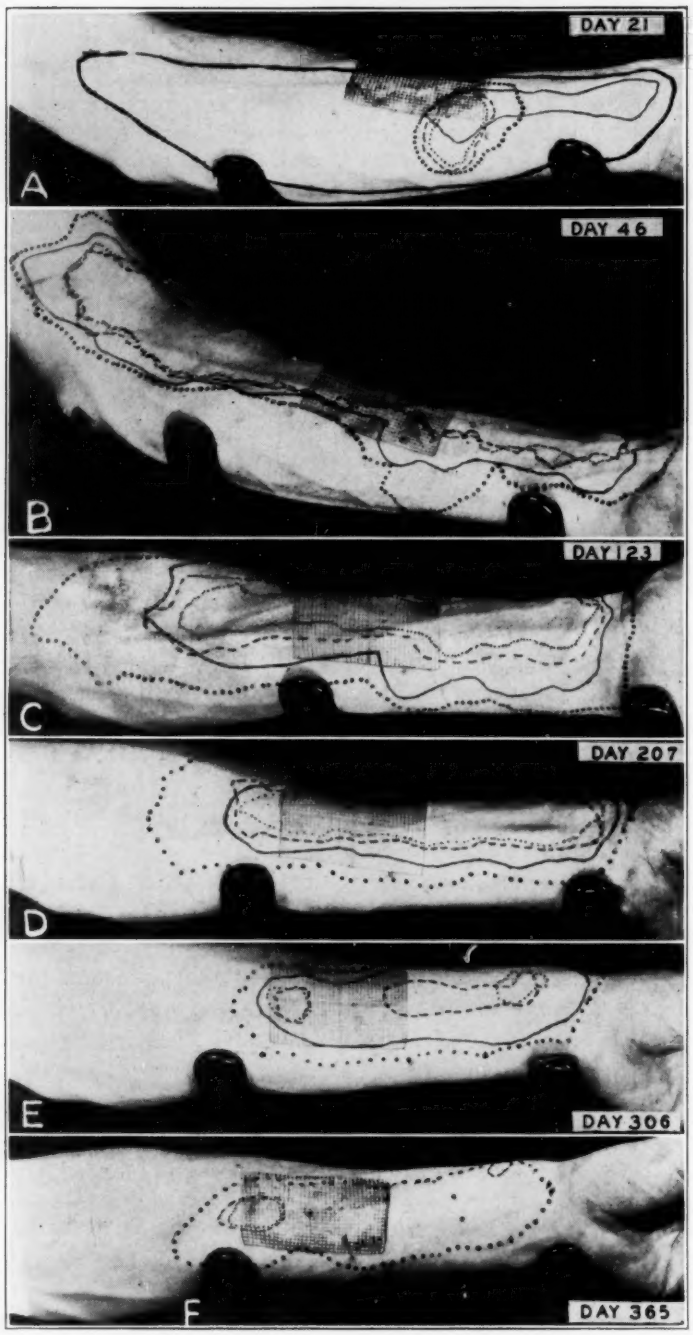

Fig. 9.—Ulnar view of arm of W. *A*, outlines of anesthesia produced by injecting alcohol into the radial division of the medial antebrachial cutaneous nerve (first operation). *B* to *F*, showing outlines of anesthetic areas and the order of return of sensation after the second operation in which alcohol was injected into the radial and ulnar divisions of the lateral antebrachial cutaneous nerve. The days are counted from the day of the first operation; the second operation was performed twenty-two days later.

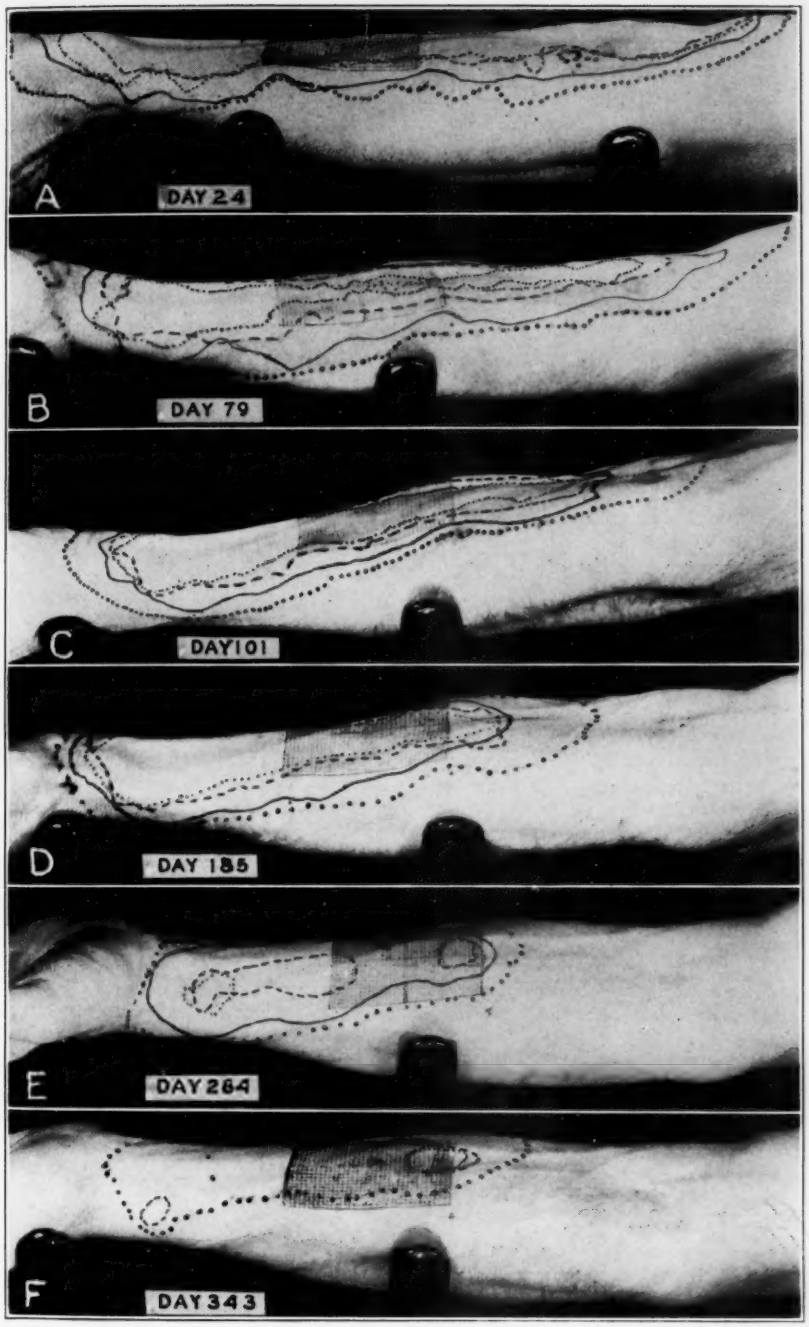

Fig. 10.—Radial aspect of W's arm, showing outlines of anesthetic areas and order of return of sensation. All these mappings were made after the second operation; each photograph is dated from the latter.

nerve; to the right of this area lies the isolated normal zone innervated by the radial branch of that nerve but deprived of accessory nerve supply from both sides; the blank squares to the right of this zone represent the area of anesthesia produced by blocking the ulnar and radial branches of the lateral antebrachial cutaneous nerve. In the lower cross-section the small sensitive zone near the radial border of the rectangle is a part of the triangular area which possessed sensitivity to touch but lacked sensitivity to pain (fig. 3 *B*). The heavy vertical lines running through each cross-section mark the lateral limits of the stamped rectangle, and from them the locations of these sections in the photographs of the arm can be easily determined.

The status of residual touch and pain sensitivity in the intermediate zones is represented in the relevant portions of figure 11 *A* and *B* (touch) and figure 12 *A* and *B* (pain). The outstanding fact revealed by inspection of the charts is that there is no sharp line of demarcation between anesthetic and normal skin. Increasing degrees of hypesthesia are manifested on proceeding from normal skin to the limits of complete anesthesia. It is apparent from figure 11 *A* and *B* that this generalization holds for touch no less than for pain, a fact which contradicts Head's observations. There can be little doubt that the intermediate zone possessed tactile sensitivity as well as sensitivity to pain, although both were defective. In fact, a comparison of the thresholds for these intermediate zones indicates that sensitivity to touch was better than that to pain. A census of the number of reactions to each type of stimulus yields the following figures: (1) touch reactions (fig. 11 *A* and *B*)—C, 206; L, 245; W, 167; (2) pain reactions (figs. 12 *A* and *B*)—C, 150; L, 203; W, 147. Combining the figures for all the subjects, the total number of touch reactions is 618, while the number of pain reactions is 500. These results contradict both Head's contention that the intermediate zone is devoid of touch sensitivity and Pollock's view [12] that nerve overlap is more extensive for pain than for touch fibers. The discrepancy between our results and those of these two investigators is probably due to differences in methods. The cotton-wool and light hair stimuli used by them were no doubt inadequate stimuli in the hypesthetic intermediate zone. Head's claim that heavier stimuli would affect the deep pressure system is invalid, since these stimuli evoked no reactions in areas of tactile anesthesia.

An examination of figures 11 *C* and *D*, and 12 *C* and *D* reveals an even more striking disparity in the efficiency of the touch, as compared with the pain, mechanisms in the intermediate zone. Whereas the thresholds for touch remain almost unchanged in comparison with the data in 11 *A* and *B*, a remarkable increase in the thresholds for

12. Pollock, L. J.: Nerve-Overlap as Related to the Relatively Early Return of Pain-Sense Following Injury to Peripheral Nerves, J. Comp. Neurol. **32**:357, 1920.

pain is observed. Furthermore, this loss of acuity extended to skin which was apparently normal in the preceding tests. Especially striking was the virtual disappearance of sensitivity to pain on the segment of L's arm innervated by the radial branch of the medial antebrachial cutaneous nerve into which no injection of alcohol was made. Inspection of the remaining charts in the series presenting the thresholds for pain shows that the lowered pain acuity of this normal skin persisted long after sensitivity had returned to formerly analgesic areas.

As a result of nerve regeneration the acuity of the touch and the pain mechanisms gradually returned to a normal level, both in the intermediate zones and in formerly analgesic areas. In the case of pain, the final charts in the series indicate hypernormal acuity. Touch sensitivity apparently reached a normal level somewhat in advance of that for pain, especially in the intermediate zones, which, as already indicated, lagged behind the analgesic areas in recovery of acuity. In the case of touch it is interesting to note that in the early stages of recovery the thresholds were high, indicating deep hypesthesia, a fact which is discordant with Head's theory.

In order to exhibit more concisely the general pattern of changes in sensitivity manifested during nerve regeneration tables 2, 3 and 4 have been prepared. The tables are based both on data relating to the thresholds shown in the charts and on additional measurements of thresholds made at intervening periods. Only results for L are given in the tables for the following reasons: (1) the tests in his case were made more frequently, (2) all classes of cutaneous areas were available on his arm and (3) lack of space prevents the inclusion of analogous material for all three subjects. Tables similar to those shown have been constructed for all the areas, however, and the results presented for L are representative of the patterns of changes in sensitivity found both in other areas on his arm and in analogous areas on the arms of the other subjects. No averaging of results was possible for different areas either on the arm of the same subject or on the arms of different subjects, since the conditions of the tissues could not be assumed to be homologous in either instance. In general, three classes of areas may be distinguished, exclusive of normal skin: (1) intermediate zones, (2) anesthetic zones and (3) mixed areas, such as L's triangle, which was anesthetic to pain stimuli but sensitive to touch stimuli. The definition of an anesthetic zone was somewhat arbitrary, in view of the inconstancy of the border from time to time. The criterion adopted for purposes of summarizing the results in the tables was "insensitivity to the maximum threshold pressures for the first two tests following the second operation."

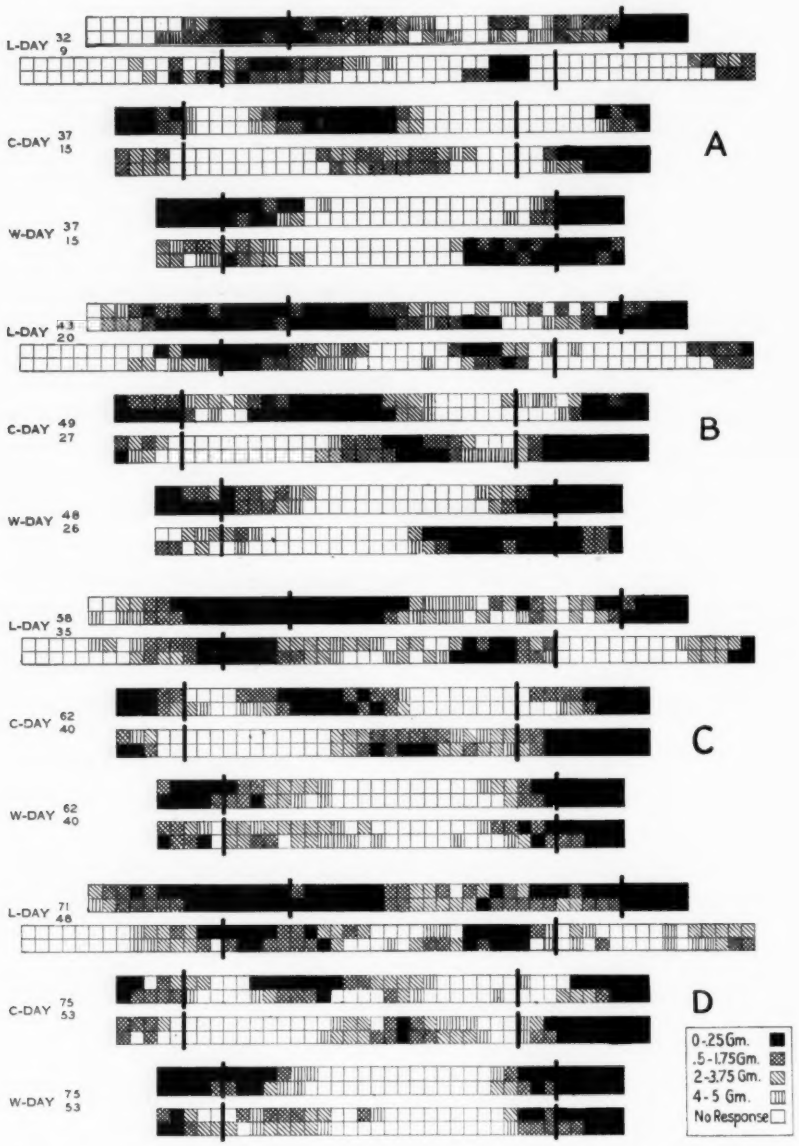

Fig. 11.—Thresholds for contact measured on two representative sections across the volar surface of the arm of each subject (see text for locations). The small subdivisions represent the 2 mm. squares which were stamped on the arm. The two heavy vertical lines in each section indicate the ulnar and radial limits of the rectangle. The left side of each figure represents the ulnar side of the arm; the right represents the radial. The subject and the dates from the day of the first and second operations are indicated at the left.

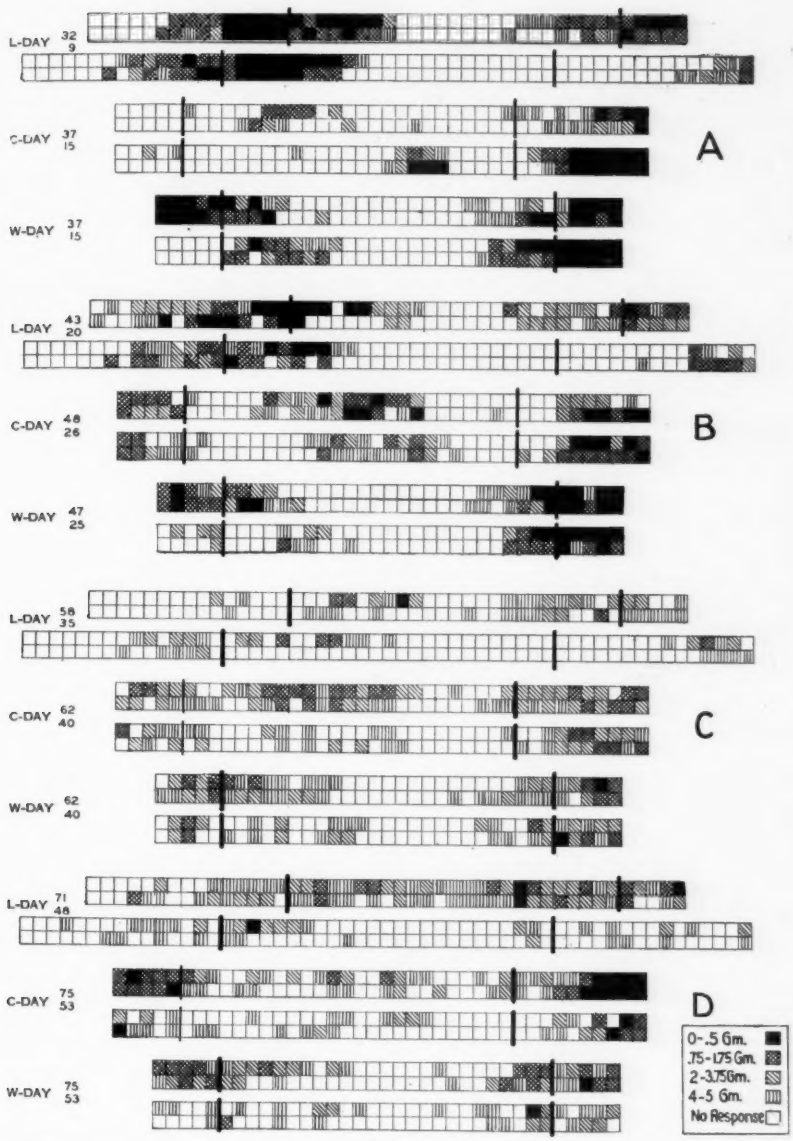

Fig. 12.—Thresholds for pain corresponding to the thresholds for contact shown in figure 11. Identical areas of skin were involved and approximately the same dates were noted in both sets of measurements.

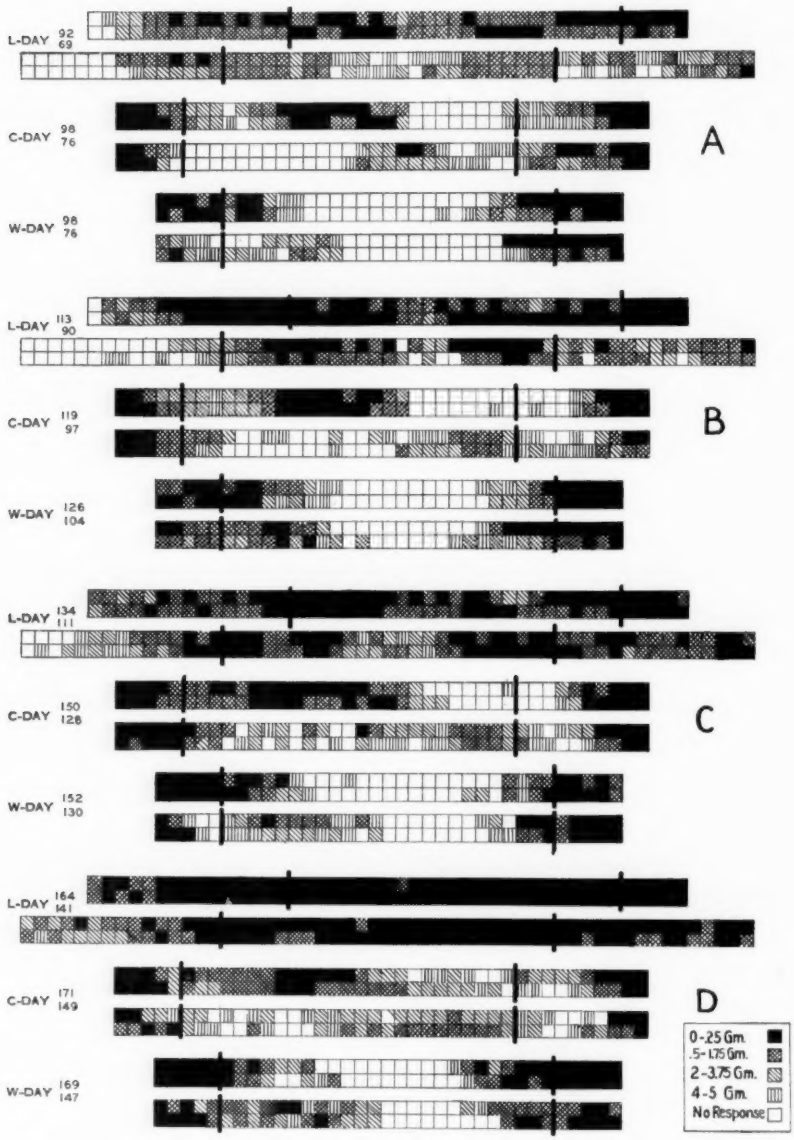

Fig. 13.—Continuation of the series showing the thresholds for contact.

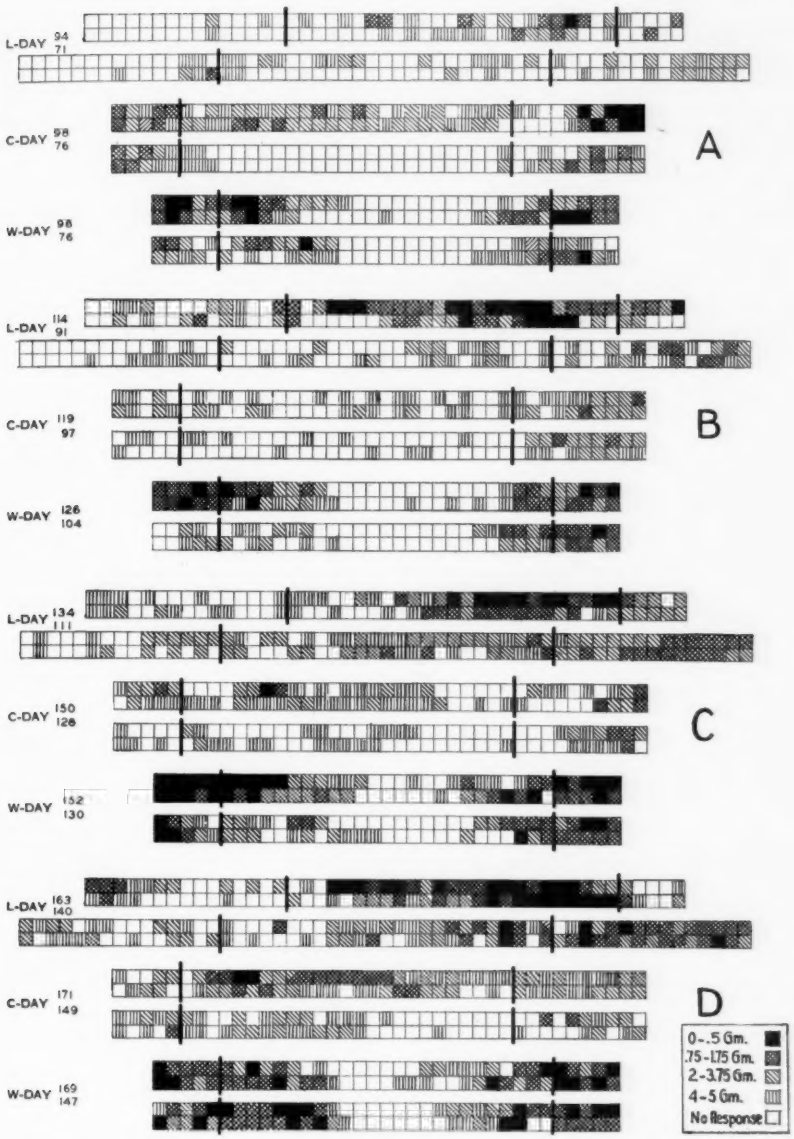

Fig. 14.—Thresholds for pain corresponding to those shown for contact in figure 13.

Table 2 contains a summary of the data on the thresholds for touch and pain for L on the part of the upper cross-section which extended from the radial limit of the anesthetic ulnar zone, across the normal skin innervated by the radial branch of the medial antebrachial cutaneous nerve to the ulnar boundary of the radial anesthetic zone. The values

TABLE 2.—*Thresholds for Touch and Pain on an Area Deprived of Accessory Innervation from Both Sides (Subject L)* *

	Thresholds for Touch, Gm.											
Day	A	B	C	D	E	F	G	H	I	J	K	L
9	0.0	0.0	4.0	2.1	0.5	0.1	0.4	0.4	0.2	0.5	2.3	5.3
20	1.1	0.5	0.2	0.4	0.1	0.2	0.8	0.2	0.2	0.5	1.1	3.2
35	2.5	0.6	0.2	0.2	0.1	0.1	0.1	0.2	0.1	0.3	2.5	3.9
48	1.2	0.4	0.2	0.1	0.1	0.1	0.3	0.1	0.2	0.5	1.5	2.2
69	1.8	0.8	0.5	0.5	0.5	0.4	0.5	0.4	0.3	0.5	0.9	0.8
90	1.7	0.5	0.2	0.2	0.1	0.1	0.2	0.3	0.2	0.3	0.8	0.9
111	1.4	0.6	0.4	0.6	0.6	0.2	0.2	0.2	0.1	0.3	1.0	0.5
141	0.6	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.2	0.2	0.3	0.2
175	0.3	0.3	0.2	0.2	0.1	0.1	0.2	0.1	0.2	0.3	0.3	0.2
205	0.2	0.3	0.2	0.2	0.1	0.1	0.1	0.3	0.2	0.2	0.3	0.3
238	0.3	0.3	0.2	0.2	0.1	0.2	0.3	0.5	0.2	0.2	0.2	0.2
266	0.2	0.2	0.1	0.1	0.2	0.2	0.1	0.2	0.2	0.3	0.2	0.4
294	0.1	0.2	0.2	0.2	0.1	0.1	0.2	0.1	0.1	0.2	0.2	0.2
322	0.1	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.2
351	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
444	0.2	0.1	0.2	0.2	0.1	0.1	0.3	0.1	0.1	0.1	0.1	0.3
520	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.3	0.1	0.2
695	0.2	0.1	0.3	0.2	0.1	0.1	0.2	0.1	0.2	0.1	0.2	0.2

	Thresholds for Pain, Gm.									
	A	B	C	D	E	F	G	H	I	J
9	5.9	3.3	1.2	0.7	0.6	0.9	1.5	1.0	1.3	4.3
20	2.8	1.9	0.7	2.4	0.4	1.8	4.6	3.1	3.5	4.2
35	0.0	0.0	5.0	5.8	0.0	5.8	4.1	4.9	4.8	3.9
48	4.8	5.8	4.4	3.9	4.8	3.8	2.8	4.0	3.6	3.9
71	0.0	0.0	4.9	0.0	5.6	5.5	0.0	5.8	3.1	5.5
91	0.0	3.9	3.7	5.3	4.1	3.8	3.6	3.1	2.5	0.9
111	4.8	5.3	0.0	5.3	5.1	5.1	5.1	5.6	5.5	3.1
140	4.8	0.0	5.0	5.0	5.3	5.1	4.4	2.3	1.4	1.6
175	2.4	5.0	3.9	5.1	4.8	4.1	4.1	0.6	1.2	3.8
204	0.3	0.4	3.0	4.1	3.5	4.6	3.6	2.1	0.9	1.2
238	0.3	0.7	0.5	1.9	4.7	3.4	1.3	0.2	0.7	0.2
266	0.2	0.3	0.3	1.7	1.8	2.6	1.3	0.2	0.5	0.3
296	0.3	0.4	0.4	0.6	4.8	4.1	2.8	0.8	0.4	0.3
322	0.1	0.2	0.3	0.3	1.6	0.2	3.3	0.3	0.2	0.2
351	0.1	1.3	0.2	0.2	3.5	1.8	2.6	0.8	1.5	0.7
444	0.2	1.8	0.3	0.6	3.2	0.3	1.1	1.3	0.4	0.3
520	0.2	0.3	0.5	0.8	0.9	0.4	0.3	0.3	0.3	0.2
695	0.3	0.6	0.5	1.6	1.8	1.2	4.4	1.9	0.4	0.4

* Each value is an average of four measurements (Gm.) in four adjacent 2 mm. squares. The thresholds for touch and pain on normal skin were 0.17 and 1.55 Gm., respectively. The areas in the table run from the borders of the anesthetic area in the ulnar, to those of the anesthetic area in the radial, portion of the arm. The dates are reckoned from the day of the second operation.

for the thresholds in the table were secured, therefore, in an isolated area of skin each of the lateral margins of which constituted an intermediate zone. In the upper half of the table the areas lettered A, B, C, etc., are successive 4 mm. squares, area A representing the ulnar, and area L the radial, side of the segment of skin. Measurement on only ten such areas was necessary to obtain the data on the thresholds for pain given in the lower half of the table. Each value in the table is an

average of four measurements secured in four adjacent 2 mm. squares. In computing these averages an arbitrary value of 6 Gm. was assigned to each square in which no response occurred; hence, when an average greater than 5 occurs this means that no response was elicited in one or more of the four squares involved. Zero indicates that no response occurred in any one of the four squares.

A study of the data on the thresholds for touch in the first row of table 2 shows clearly the existence of gradations of sensitivity in the intermediate zone. Thresholds were high near the anesthetic borders and gradually decreased as normal skin was approached. As time passed, presumably bringing nerve regeneration to adjacent anesthetic areas, the hypesthesia of the intermediate zone gradually declined. The sudden drop in the thresholds of areas B to D is unusual and atypical, as judged by the results shown for areas J to L and by figures for four other intermediate zones. It should be noted that the practice of mechanically averaging thresholds secured in four adjacent 2 mm. squares may often be unjustified, since the intermediate zone varies widely in extent even at different places along the course of the same nerve branch; and if, for example, this zone between normal and anesthetic skin were only 4 mm. wide or less, gradations of the sort usually found would be obscured entirely by such averaging. One such narrow intermediate zone was observed on W's arm.

The results for pain stimuli in the lower half of the table manifest a pattern strikingly different from that for touch stimuli. This difference, which is noted in the comment on the charts, consists principally in a great reduction of acuity, both in the intermediate zone and in normal skin, beginning at about the fifth week. The return of normal pain acuity began at the borders of the anesthetic areas and gradually spread inward to the skin the primary nerve supply of which was unaffected in the operations. The skin bordering the anesthetic areas not only regained normal acuity but passed into a stage of hyperesthesia. This condition spread gradually inward toward the hypesthetic normal skin lying between the two denervated areas.

The patterns of changes in acuity exhibited by denervated areas during recovery are shown in table 3. As an entire anesthetic segment of a given cross-section might be considered somewhat homogeneous with respect to innervation at any given time, the average of all the values secured in such a segment is used as its index of sensitivity. The thresholds for touch, shown in the first half of table 3, gradually decline with time, indicating a progressive reduction of hypesthesia with nerve-regeneration. This trend is characteristic of all the anesthetic areas studied, with the exception of W's small zone which failed to regain sensitivity to touch or pain (fig. 9 *E* and *F*).

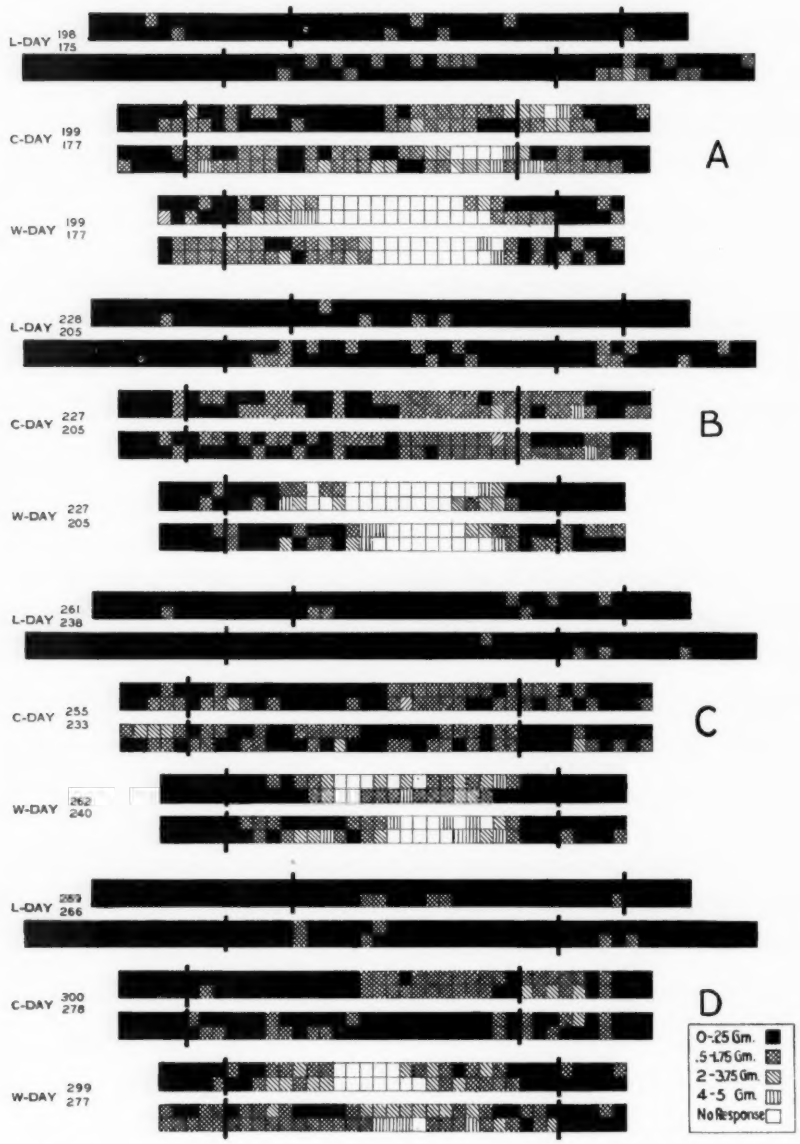

Fig. 15.—Continuation of the series of the thresholds for contact on the affected areas.

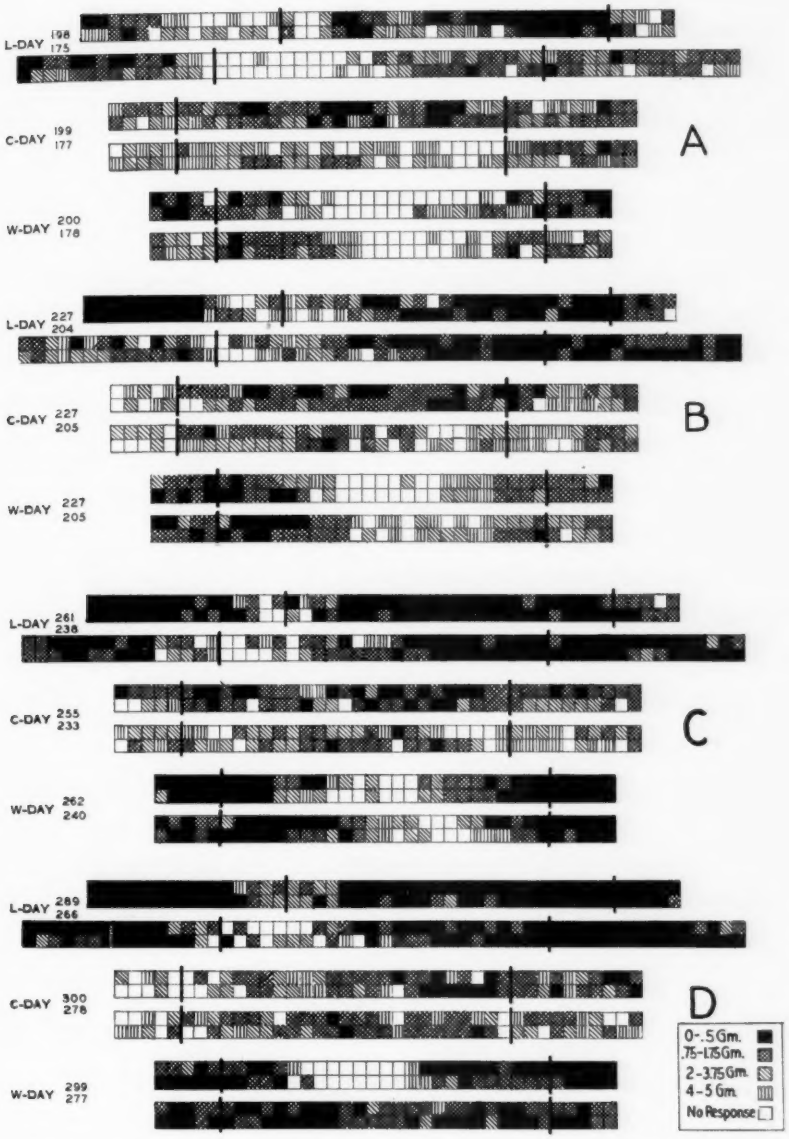

Fig. 16.—Thresholds for pain corresponding to those shown for contact in figure 15.

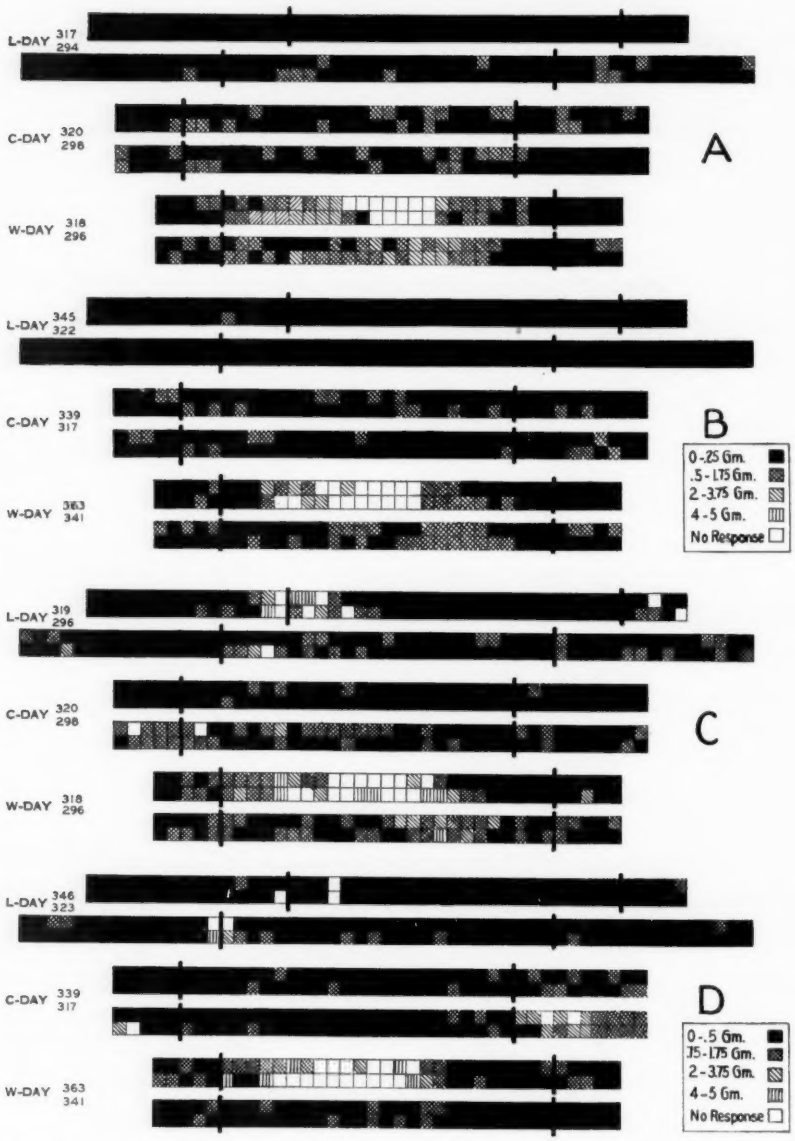

Fig. 17.—*A* and *B*, thresholds for contact (end of series); *C* and *D*, thresholds for pain (end of series).

The thresholds for pain manifest the same general pattern of changes, except that after a normal acuity level was reached a condition of hyperesthesia developed. A comparison of the rates of restoration of sensitivity to contact and to pain reveals that the thresholds for contact tend to approximate to the preoperation level earlier than those for pain. As was noted in the discussion of the charts, this fact is at variance with expectations based on Head's theory.

A comparison of the thresholds for touch and pain secured in L's triangle is made in table 4. This area, like Head's small dissociated triangle, responded to light contact but not to prick. The limens for

TABLE 3.—*Thresholds for Touch and Pain on Anesthetic Areas, Showing Return of Sensation Due to Nerve Regeneration (Subject L)* *

Thresholds for Touch, Gm.			Thresholds for Pain, Gm.		
Day†	Section 1 (16 Mm.)	Section 2 (12 Mm.)	Day†	Section 1 (40 Mm.)	Section 2 (12 Mm.)
32- 9	0.0	0.0	32- 9	0.0	0.0
43- 20	5.9	5.6	43- 20	0.0	0.0
58- 35	5.9	4.0	58- 35	5.9	5.8
71- 48	5.4	4.1	71- 48	5.7	4.5
92- 69	3.6	3.9	94- 71	5.3	5.0
113- 90	2.7	2.9	114- 91	4.9	1.2
134-111	0.8	1.2	134-111	3.2	1.9
163-140	0.3	0.2	163-140	2.7	1.3
198-175	0.5	0.3	198-175	2.2	2.0
228-205	0.3	0.5	227-204	0.9	1.1
261-238	0.2	0.1	261-238	1.0	0.3
289-266	0.2	0.1	289-266	0.8	0.6
317-294	0.3	0.2	319-296	0.4	0.2
345-322	0.2	0.1	345-322	0.3	0.1
374-351	0.1	0.1	374-351	0.5	0.6
467-444	0.3	0.1	467-444	0.3	0.2
543-520	0.5	0.1	543-520	0.6	0.2
718-695	0.4	0.1	718-695	0.3	0.6

* Each figure represents an average threshold for the entire cross-section of an area, the width in millimeters of which is indicated by the number in parentheses. Zero means no response. The values are given in grams.

† The days are counted from the day of the first and from that of the second operation, respectively.

touch indicate that the area was hypesthetic along the margins adjacent to anesthetic skin, although not as markedly so as other intermediate zones; the middle of the area was practically normal. Pain sensitivity was entirely absent for more than seven weeks after the second operation. Its return was characterized by the same pattern of changes in the threshold observed in other anesthetic areas: deep hypo-algesia, gradual return to a normal level, hyperalgesia.

QUALITATIVE CHANGES IN SENSITIVITY

The foregoing results on changes in sensitivity have related only to alterations in the quantitative measurements of the thresholds. This approach neglects, however, what Head regarded as the most striking sensory consequences of nerve division, namely, unpleasant pain, cold

and warmth and abnormal localization. He believed that these protopathic phenomena are inhibited by the regeneration of the epicritic fibers. Unfortunately, Head presented no factual results concerning these phenomena other than general clinical descriptions. Boring properly recognized the necessity for systematic observation of definite areas and for quantification of the subject's reports. Boring was, however, more interested in introspective analysis of the various types of protopathic experience than in possible temporal variations in the pattern presented by his estimates of the intensity or the quality of sensation. He merely averaged his sensitivity indexes, thereby precluding a detailed analysis of the qualitative variations observed. Our estimates of quality

TABLE 4.—*Measurements of Threshold for Touch and Pain for L's Triangular Area, Which Was Anesthetic to Pain, But Sensitive to Contact Stimuli* *

Day†	Thresholds for Touch, Gm.			Thresholds for Pain, Gm.		
	A	B	C	A	B	C
32- 9	1.3	0.4	2.3	0.0	0.0	0.0
43- 20	3.8	1.1	1.4	0.0	0.0	0.0
58- 35	1.9	0.2	0.3	0.0	0.0	0.0
71- 48	1.9	0.2	0.3	4.1	0.0	0.0
94- 71	0.8	0.9	1.3	5.0	5.1	5.8
114- 91	1.9	0.3	0.8	0.0	2.3	5.1
134-111	0.3	0.2	0.3	3.6	3.2	4.6
163-140	0.1	0.2	0.2	3.1	1.5	2.7
198-175	0.1	0.1	0.3	2.5	1.3	1.3
227-204	0.1	0.1	0.3	0.2	0.6	0.3
261-238	0.1	0.1	0.1	1.6	0.5	0.3
289-266	0.1	0.1	0.1	0.7	0.5	0.4
319-296	0.1	0.1	0.3	0.3	0.4	0.4
345-322	0.1	0.2	0.2	0.3	0.2	0.1
374-351	0.1	0.1	0.2	0.4	0.3	0.3
467-444	0.1	0.1	0.1	0.3	0.2	0.2
543-520	0.1	0.1	0.1	0.3	0.4	0.9
718-695	0.1	0.1	0.2	0.3	0.3	0.3

* Zero indicates that no response occurred. The values are average thresholds (Gm.) for areas of 4 mm. square which are lettered A, B and C.

† The days are counted from the day of the first and from that of the second operation, respectively.

or intensity of response cannot, therefore, be compared with results of previous investigators. The supplementary diary records supply a general account of changes in sensitivity comparable with the reports found in the earlier studies.

1. Sensitivity to Incidental Contact.—The intermediate zone about an anesthetic area began to show hypersensitivity to stroking within from four to twelve days after injection into the nerve, the time varying in the three subjects. It was manifested first as a sort of live, unpleasant sensation, devoid of pain; the sensations gradually increased in intensity, developing in certain places a raw quality resembling the effects of stroking a bad sunburn. Although the entire border appeared to possess this protopathic sensitivity, systematic stroking revealed that it was concentrated in certain areas, with a lack of normal sensitivity on intervening skin. This hypersensitive condition disappeared before nerve regeneration occurred in the adjacent anesthetic skin, a fact which agrees with the account of Trotter and Davies.

With the disappearance of this initial hyperesthesia the intermediate zone was decidedly hypesthetic to stroking and to other areal contact stimulation. These areas felt dull in comparison with normal skin. This dulness persisted until nerve regeneration produced a second type of hypersensitivity both in formerly anesthetic areas and in marginal zones. The new hyperesthesia took the form of fluttery, unpleasant sensations which appeared first along the course of the nerve in the affected area. The flutter felt much like the effects of stroking stiff hairs, although it was present after the arm was shaved. The effect was, however, much more intense and disagreeable than that produced by stroking normal hairy skin. This tingling response had not disappeared entirely from all the affected areas even after three years. This abnormal response is probably what Head calls "hair sensibility" and represents a protopathic stage of sensibility to touch. The term protopathic as used here is merely descriptive and does not imply a special neural mechanism.

TABLE 5.—*Changes in Qualities of Touch Sensation in Typical Intermediate and Anesthetic Zones of Subject L* *

	Intermediate Zone, Percentage				Anesthetic Zone, Percentage			
Day†	1	2	3	P	1	2	3	P
32- 9	16	7	6	..	..	..	..	..
38- 15	8	5	18	15	..	..	..	..
58- 35	18	25	35	3	11	21	..	..
94- 71	13	27	40	..	25	21	25	..
114- 91	23	13	33	..	25	21	28	3
134-111	35	18	35	5	21	36	25	..
163-140	38	13	35	8	61	14	11	..
198-175	48	35	13	..	50	32	14	..
261-238	65	13	22	..	78	11	11	..
319-296	35	43	20	..	43	21	18	..
345-322	32	23	23	..	46	25	25	..
467-444	45	38	17	..	61	25	14	..
543-520	55	20	15	..	57	29	11	..
718-695	36	46	18	..	50	18	18	..

* The values are the percentages of the total number of stimulations on a given day. The symbols 1, 2, 3 and P refer to light touch, dull pressure, sharp touch and protopathic touch, respectively.

† The days are counted from the day of the first and from that of the second operation, respectively.

2. *Changes in Sensitivity to Punctiform Touch.*—Tactile hypesthesia, in terms of the stimulus threshold, was found to exist both in the intermediate zones and in formerly anesthetic areas during the early stages of recovery (tables 2 and 3). The present problem concerns the pattern of changes in the quality or intensity of touch sensation in such areas. As already mentioned, we distinguished three types of touch sensation on normal skin: light touch, pressure and sharp touch. Following denervation only one new designation was added to this list, namely, hypersensitive or protopathic touch, which refers to a live, bright touch sensation. This did not occur frequently and was usually unpleasant.

The pattern of qualitative changes in touch sensibility can be observed in the figures shown in table 5. This table contains the percentages of different types of touch sensations in a typical intermediate zone and in a formerly anesthetic area. These estimates of quality and intensity were made in connection with the determination of the limens. The symbols 1, 2, 3 and P refer to light touch, dull pressure, sharp touch and protopathic touch, respectively. The percentages are based on the total number of stimulations per unit area rather than on the number

of responses elicited. The results in the case of the intermediate zone show that tactile hypesthesia existed after denervation. This condition is indicated not merely by the fact that only 29 per cent of the spots stimulated yielded touch sensation (many others gave pain sensations) but also by the absence of live touch and the scarcity of sharp touch reactions. At the next sitting, however, a definite change was observed in the proportions of the several touch qualities elicited. Many more sharp and protopathic touches were reported than light touch or dull pressure sensations. As recovery proceeded there were a reduction in this hypersensitivity and a closer approximation to the proportions of cutaneous qualities observed on normal skin. On the latter, at a pressure of 0.25 Gm., the figures for light, dull and sharp touch reactions were 45, 25 and 15 per cent, respectively; 13 per cent of the stimulations on normal skin evoked no response, and 2 per cent produced pain. (These figures represent the averages for all three subjects.)

The pattern of changes in the proportions of the different touch qualities during the return of sensation on an area formerly entirely anesthetic is shown in the second part of table 5. The figures representing the percentage for the four types of touch sensation show that hypesthesia characterized the early stages of recovery. This condition changed to hyperesthesia at about the twelfth week; this was in turn followed by a gradual return to a sensory condition similar to that of normal skin.

It should be noted that these judgments, considered individually, are highly unstable, have no absolute significance and at best can indicate only gross alterations in the character of the sensory reactions elicited during changing conditions of innervation. Furthermore, the normal touch qualities, represented by the symbols 1, 2 and 3, were often somewhat different from analogous sensations on normal skin, although the differences are difficult to describe or classify. In many cases the difference seemed to consist in a lowered intensity or brightness of the sensations in the affected areas. The hypersensitive spots were irregular in distribution and were often found adjacent to spots yielding sensations of greatly reduced intensity. Furthermore, on recovering areas the responses to touch were frequently followed by pain, although the longer latency of pain usually permitted the discrimination of the two types of sensation readily. In many instances pain was felt without an intervening touch sensation.

Peripheral reference of touch sensation was observed by all three subjects, although this phenomenon was rare. The reference was as definite for touch as for pain, however, and certain spots consistently yielded referred touch sensations for several months.

3. Qualitative Changes in Pain Sensitivity.—The general trend of changes in the intensity and quality of pain in typical intermediate and anesthetic areas is shown in table 6. The values in the table are the percentages of protopathic and of normal pain sensations of the various intensities for typical areas on L's arm. The normal pain sensations were like the bright pain reactions secured on normal skin; protopathic pain was an extremely uncomfortable itching pain which radiated over a wide area and tended to provoke reflex withdrawal of the arm and scratching. This category probably corresponds to Boring's "wicked pain." This itching pain was not the only type of pain encountered which was qualitatively unlike normal pain, although it was by far the most common. Occasionally, explosive, intense pains were felt, especially during nerve regeneration. All types of pain which seemed different from normal cutaneous pain were classed as protopathic. This category also includes referred pains, although the latter were often normal in character and might have been so classified.

It is apparent from the data in table 6 that hypersensitivity existed in the intermediate zone shortly after denervation, although the sensitivity of the area, in terms of the threshold and of the total number of responses, was markedly reduced. Whereas on normal skin 93 per cent of the stimulations of a pressure of 1 Gm. elicited pain, the average figure for all types of pain reactions for the thirty-second day was only 76 per cent. (The corresponding average for all three subjects was 68 per cent.) Furthermore, the intensity of the stimulus necessary to excite pain was greatly increased, as the data on the threshold showed. Despite this reduced efficiency of the area, the spots which did respond yielded a high proportion of protopathic pain reactions, and the normal pains were preponderately of the "three" variety. On normal skin, at a pressure of 1 Gm., the proportions of reactions falling in the three intensive categories were as follows: "one," 32; "two," 37; "three," 24.

TABLE 6.—*Qualities and Intensities of Pain Sensation Elicited in Typical Intermediate and Anesthetic Zones (Subject L)* *

	Intermediate Zone, Percentage						Anesthetic Zone, Percentage					
	Normal			Protopathic			Normal			Protopathic		
Day†	1	2	3	1	2	3	1	2	3	1	2	3
32	8	13	3	16	21	15	..	..	..	..	..	..
38	22	15	5	3	10	3	..	..	..	..	..	..
58	20	3	..	..	..	..	3	..	3	..	..	..
94	17	10	..	..	..	..	10	8	10	3	..	..
114	25	3	..	..	8	..	23	10	3	5	5	3
134	43	17	..	..	..	..	27	30	8	10	13	3
163	27	13	3	5	..	..	25	23	3	20	17	..
198	35	5	..	8	3	..	32	10	..	40	8	..
261	45	10	..	..	20	..	30	30	..	22	10	..
319	30	5	3	20	35	3	13	15	5	28	35	3
345	18	12	..	25	38	5	18	..	..	52	28	3
467	35	10	..	35	18	2	20	15	3	22	30	10
543	45	10	2	13	25	..	12	18	10	20	33	7
718	65	5	..	15	10	..	30	38	15	10	7	..

* "Normal" and "protopathic" refer to different pain qualities; the symbols 1, 2 and 3 represent different intensities of pain. The values are percentages of the total number of stimulations in the area on the day indicated.

† The days are counted from the day of the first operation.

About six weeks after the second operation both the number and the intensity of pain reactions in the intermediate zone became markedly reduced, corresponding to the increase in the thresholds already noted. The protopathic reactions practically disappeared, and the intensity of the normal pains was predominately of the "one" variety (mild pain). After intervals which varied considerably in the three subjects there was a return of hypersensitivity, presumably coincident with the ingress of regenerating nerve fibers into the intermediate zone from the adjacent nerve. This second peak of hypersensitivity was characterized especially by protopathic pain responses along the borderline of the affected area. As regeneration progressed there was a tendency to a second reduction of the intensity of pain reaction in the intermediate zone. This pattern of changes in sensitivity was observed in all three subjects.

The changes in estimated intensity and quality of pain on a typical recovering area (formerly entirely anesthetic) are shown in the second part of table 6. The most extensive anesthetic cross-section available was used. The earliest pain reactions in the area indicated definite hyposensitivity. The pain usually was mild and similar qualitatively to normal pain, although the pressure required to elicit

it was greater. (Only C reported protopathic pain in the earliest stages of recovery, and this was absent for several successive weeks thereafter). As regeneration proceeded the area yielded more and more protopathic reactions, as well as more type "two" reactions of the normal variety. After almost two years the hyperalgesia began to recede, and the sensory condition of affected areas approximated more nearly that of normal skin. The protopathic types of pain reactions were numerous especially along the large veins, near which ran the main branches of the regenerating nerves. It should be noted that the intensity symbols "one," "two" and "three," which we applied to the protopathic reactions, imply that these responses were not of the "all-or-nothing" variety, as Head contended. Many of the reactions occurred suddenly with almost unbearable intensity, but the itchlike extremely uncomfortable pains, which constituted by far the majority of our protopathic type, more often developed gradually and with perceptibly different degrees of intensity.

Peripheral reference of pain sensation, one of the most unusual phenomena of abnormal sensibility, was restricted mainly to two of the subjects, C and L (W reported only two definitely referred pains during the experiment). It is impossible to compare the proportions of referred sensations observed in the present experiment with the results of preceding investigators, since no figures were given by any of the latter. The percentage of referred pains was much lower than one would expect from Head's descriptions, the maximum figure being 22 per cent for C on the hundred and seventy-first day after the first operation and the hundred and forty-ninth day after the second. On only three occasions did the figure for referred pains exceed 10 per cent. In general, there was relatively more reference in the earlier stages of nerve regeneration than later. No explanation can be given of the almost complete absence of peripheral reference in W.

4. Touch and Pain Sensitivity in the Triangle.—Head asserted that when his dissociated epicritic triangle regained pain sensibility the usual protopathic aspects of returning pain were absent. L's large triangular area, which never lost touch sensibility, was studied carefully with a view to checking Head's observations on this point, since confirmation of these is especially crucial in substantiating his theory. We have already noted that the pattern of changes in the threshold for pain in the triangle was similar to that in other recovering areas.

The results shown in table 7 constitute a striking contradiction of Head's observations. The first half of the table gives the figures for the percentages of the several types of touch sensation; the second half shows analogous figures for pain. The data on touch are interesting in showing an unusually high proportion of type "one" reactions, representing normal light touch, and, later in the course of nerve regeneration, a considerable number of the hypersensitive protopathic reactions. But returning pain sensibility manifested in a striking fashion the pattern observed in other recovering areas, namely, hypalgesia, hyperalgesia, normal sensitivity. The abnormal, protopathic pains in this area were fully as intense and unpleasant as those observed in any other recovering area. Peripheral reference of pain was also observed in this triangle.

5. Changes in Thermal Sensitivity.—With the exception of a series of punctiform examinations for cold sensitivity in typical recovering areas in the case of L, the records of changes in cold and warmth sensitivity consist primarily of diary notes based on the outlining of zones of thermal anesthesia. In connection with this work, rough comparisons of the quality and intensity of cold and warmth on normal, marginal and recovered zones at varying stages were made.

The observations on cold sensitivity for L agree substantially with those of Boring in indicating that in the early stages of recovery the reaction to cold was somewhat hypesthetic. This condition changed fairly rapidly to hyperesthesia, which was manifested in the form of a sensation of deep intense cold, as well as in the increasing number of spots responding to cold stimuli. In certain areas, almost every stimulus elicited a response (the seventy-ninth day after the first operation and the fifty-sixth day after the second), in agreement with Boring's results. Many of these sensations were referred peripherally, especially those elicited by stimulation applied along the course of the regenerating nerve trunk. By the hundred and eighty-eighth day after the first operation and the hundred and sixty-fifth day after the second (subject L) the referred sensations were greatly reduced in number and the proportion of sensations of normal quality and intensity had greatly increased. At the time of writing, three years after the experiment, cold

TABLE 7.—*Changes in Quality and Intensity of Touch and Pain Sensations on L's Triangle (Area Which Lost Pain Sensibility but Retained Touch Sensibility)* *

	Touch				Pain					
	Quality of Sensation				Normal			Protopathic		
Day†	1	2	3	P	1	2	3	1	2	3
71- 48	75	17	..	..	..	17	8	..	..	..
92- 69	25	58	17	..	25	8	8	..	..	..
113- 90	33	67	..	..	25	8	..	8	8	..
134-111	58	25	17	..	8	17	17	25	17	..
164-141	75	17	..	8	25	17	..	17	25	..
198-175	50	42	..	8	8	33	..	33	17	..
261-238	91	..	8	..	33	33	..	17	8	..
317-294	75	17	8	..	17	17	8	25	33	..
345-322	75	17	..	8	16	..	..	42	42	..
467-444	67	8	..	25	17	8	..	25	42	8
543-520	67	17	8	8	..	8	25	25	33	8
718-695	75	8	..	..	42	25	33	..	..	..

* The symbols 1, 2, 3 and P have the same meaning as in table 5. Likewise, the symbols 1, 2 and 3 for pain have the same meaning as in table 6.

† The days are counted from the day of the first and from that of the second operation, respectively.

sensibility is, however, still abnormal on the affected areas. Areal stimulation produces a sensation of deeper cold in spots, intermingled with sudden sensations of sparkling cold, the intensity of which often exceeds that of normal cold. But in the aggregate the affected areas are still defective in cold sensitivity, despite the hyperesthesia of individual spots. Areal stimulation produces decidedly less cold sensation than is secured on normal skin.

The return of warmth sensitivity was difficult to study by the punctiform method, since the thermesthesiometer usually produced pain on the hyperesthetic recovering areas. The pain from areal stimulation was less noticeable. In general warmth sensibility has been apparently hypesthetic ever since the beginning of recovery. Whatever hyperesthesia has been present appears to have been due to the sting (pain) accompanying the thermal sensation proper. Occasional referred warmth sensations were observed, one in particular being that of a mild warmth elicited proximal to L's rectangle and referred to the wrist. The same spot was located for several weeks. A note from L's diary on the two hundred and sixty-sixth day after the first operation and the two hundred and forty-third day after

the second describes warmth sensation on formerly anesthetic skin as follows: "Warmth sensation is difficult to elicit; the sensation is diffuse, spotty. Running the areal stimulator from the elbow to the wrist shows a striking difference between the left and right arm. On the former there is a sting, diffuse warmth and occasionally a definite spot. On the latter there is rapid succession of bright warmth sensations."

LOCALIZATION AND TWO-POINT DISCRIMINATION

1. Localization.—All previous investigators have reported that localization is neither lost nor impaired by the severance of cutaneous nerves. Our observations contradict this general dictum.

The three subjects reported that no definite local sign seemed to accompany the deep pressure stimulation in areas of cutaneous anesthesia. Even at a stimulus pressure of 15 Gm. the subject often failed to respond at all; frequently three or four stimulations were necessary before he could attempt any localizing movement. There was no "pointedness" in the impression aroused by the stimulus, a corollary of the inability to discriminate the size and shape of objects on anesthetic skin. Careful distinction should be made between the definiteness of the cues on which localization is based (the local sign of the spot stimulated) and the usual numerical indexes of efficiency in localization. It is our opinion that the latter are not at all comparable with analogous figures obtained from observations on normal skin and that in the nature of the case they may yield an accuracy index for an area of cutaneous anesthesia which does not represent the reduced definiteness of the sensory cues arising from the residual deep pressure system. When the subject is stimulated on an area of cutaneous anesthesia his attempts to touch the spot stimulated are subject to automatic correction should he place his stylus outside the area. The sensory cues from normal or marginal skin are so different from the diffuse deep pressure sensation of the anesthetic area that the subject naturally moves his localizing stylus until a similar dull area is reached. It is impossible to inhibit the operation of this and of other types of accessory cues, and consequently greater accuracy is attained by such a test than the diffuse sensory cues would seem to justify.

The results of certain of the localization tests made on normal and anesthetic skin are shown in table 8. The method employed was that of having the subject try to touch the spot stimulated. In the normal series the spot stimulated was always the center of the rectangle; for the postoperative tests ten anesthetic spots were used for both C and W, while four spots were used for L. Efficiency in localization is measured in terms of two types of errors—the constant error and the variable error. The constant error is simply the average displacement of the stylus (in millimeters) with reference to each of two axes drawn through the point stimulated, and is found by dividing the algebraic sum of the measurements by the number of trials. The variable error is the average of the variations of the individual measurements from the constant error. The variable error is thus a rough index of the reliability of the constant error. The figures for constant and variable errors in table 8 were based on all measurements made for a given subject, irrespective of differences in location of the points stimulated. A comparison of the measurements for errors in localization before and after denervation shows that all those for the variable errors were from two to four times as great for anesthetic as for normal skin, although those for the constant errors were not strikingly different.

The high figures for the variable errors explain in part the rather low ones for the constant errors. Extreme errors in opposite directions cancel each other in the computation of the constant error, whereas the variable error reflects such greater dispersion of measurements. The variable errors are especially large in the central-peripheral direction, as one would expect if capacity for localization were reduced by denervation. The lateral (radial-ulnar) extent of an area being rather narrow, the sort of correction previously mentioned would operate to limit the error in that direction.

The reduction in the capacity for localization is shown equally clearly in the results secured by the second method, in which the subject called out a number representing the point stimulated. Using the same points as in the tests just described, and with ten stimulations for each point, the following figures for correct localizations were secured approximately two weeks after the second operation: C, 52; L, 40, and W, 46 per cent. The figures for correct judgments for pressures of 15 Gm. on normal skin were 79, 84 and 61 per cent, for C, L and W, respectively.

TABLE 8.—*Errors of Localization for Normal and Anesthetic Skin* *

	Normal Skin				Anesthetic Skin		
Subject	Constant Error, Mm.	Variable Error, Mm. R-U	Variable Error, Mm. C-P	Day†	Constant Error, Mm.	Variable Error, Mm. R-U	Variable Error, Mm. C-P
C	U 0.75 C 0.30	2.16	5.95	49-27	R 1.08 P 13.84	5.13	11.13
L	U 2.44 C 10.32	1.94	4.44	45-22	R 8.30 C 3.55	3.96	15.74
W	R 1.88 P 15.44	1.46	4.50	49-27	R 1.87 P 9.65	3.84	9.65

* A pressure of 15 Gm. was used. The symbols R, U, C and P refer to radial, ulnar, central and peripheral directions from the points stimulated. The values are in millimeters.

† The days are counted from the day of the first and from that of the second operation, respectively.

The results secured by both methods of measurement indicate a definite impairment of the ability to localize stimuli of 15 Gm. on denervated skin. The sensory impulses provided by the deep pressure system mediate perception of the general body area stimulated, but differential localization is possible only within rather broad limits. The cutaneous nerves seem to be by far the most important factors in normal localization. This conclusion is further supported by the results secured on normal skin with a stimulus of a pressure of 2 Gm., which we found to be inadequate to arouse the deep pressure system in areas of cutaneous anesthesia. By the first method of testing localization the constant errors were somewhat greater with a pressure of 2 Gm. than with one of 15 Gm., but the variable errors were slightly smaller. By the second method the following figures for correct judgments were secured with a 2 Gm. stimulus: C, 78; L, 78, and W, 68 per cent. The corresponding figures for normal skin at a pressure of 15 Gm. were 79, 84, and 61 per cent.

No attempt was made to test all the subjects for localization throughout recovery, although special tests were made on W, in whom the region of tactile anesthesia was extensive and in whom recovery occurred late. The results of the measurements of localization for three points in W's rectangle are given in table 9. The points stimulated lie on the longitudinal axis of the rectangle (at the lower

end, in the middle and at the upper end). The types of errors shown for these three points are interesting in revealing that there was a considerable tendency for the subject to localize stimuli in the same general region, regardless of the point stimulated. With but two exceptions all the constant errors were found to lie in the radial-peripheral (R, P) portion of the rectangle. The differences between the constant errors for the three points indicate that some discrimination among them existed, although this was apparently slight. The variable errors are unusually high, although in the later series, in which the higher constant errors indicate a sort of stereotypy of the localizing movements, the variable errors tend to decline in size.

A third method of testing localization yielded results in agreement with the conclusion that localization on anesthetic skin was impaired, although the method was not used with any subject except W. Two stimuli were applied in succession,

TABLE 9.—*Errors of Localization for Three Points Located in Squares 4, 5 and 6 of the Rectangle (Fig. 2) for Subject W* **

	Square 4			Square 5			Square 6		
	Constant Error,	Variable Error, Mm.		Constant Error,	Variable Error, Mm.		Constant Error,	Variable Error, Mm.	
Day†	Mm.	R-U	C-P	Mm.	R-U	C-P	Mm.	R-U	C-P
49- 27	R 6.5 P 4.5	1.50	12.40	R 5.6 P 11.7	5.08	10.84	R 3.9 P 11.9	3.6	16.30
200-178	R 7.0 C 5.3	1.50	10.03	R 5.2 P 13.3	3.14	6.31	R 6.3 P 37.4	2.56	8.60
203-181	R 5.5 P 9.5	1.23	6.90	R 5.0 P 16.9	1.00	9.01	R 6.2 P 48.3	2.14	16.30
208-186	R 8.7 C 4.5	2.66	8.15	R 7.0 P 13.0	1.60	6.60	R 7.7 P 39.0	1.93	6.60
220-198	R 6.2 P 5.2	3.16	8.12	R 5.6 P 27.9	2.68	10.32	R 4.9 P 55.7	2.41	8.06

* The symbols R, U, C and P refer to radial, ulnar, central and peripheral directions from the points stimulated.

† The days are counted from the day of the first and from that of the second operation, respectively.

and the subject was asked to report whether the second point was the same or whether it was central or peripheral, with reference to the first. All the points lay on the longitudinal axis of the rectangle. The figures for correct judgments were as follows, for seventy trials at each of the separations indicated: 40 mm., 50 per cent; 50 mm., 61 per cent; 60 mm., 66 per cent; 70 mm., 80 per cent, and 80 mm., 77 per cent. Although some discrimination of relative localization obviously existed, the separations used are much higher than would be necessary to give such figures for normal skin. This subject's normal limen for two points applied simultaneously was only 32 mm.

2. Two-Point Discrimination.—This function was entirely abolished in all zones of anesthesia to touch for separations of the two points up to 80 mm. This distance was the widest separation possible with the Ebbinghaus esthesiometer. These tests were made many times on anesthetic zones, and all three subjects invariably reported only a dull, poorly localized pressure, with no suggestion of "twoness." Furthermore, the limens secured on normal skin with a pressure of 2 Gm. were only slightly greater than those secured with a pressure of 15 Gm.,

although pressures of 2 Gm. were inadequate to arouse the deep sensibility system. Our observations thus confirm those of Head, of Trotter and Davies and of Dallenbach,[13] and contradict those of Boring, in showing that two-point discrimination is mediated by cutaneous nerves. Boring failed to secure either abolition or increase in the two-point limen on his anesthetic area. The only explanation of this anomalous result which we can offer is that the heavy pressures used were activating hypesthetic, or normal, cutaneous mechanisms at the margins of Boring's small anesthetic area. Although the limens secured by him seemed to fall within his limits of anesthesia, the stimuli must have affected normal cutaneous fibers.

The two-point limens secured in the hypesthetic intermediate zone were much greater than those for normal skin; these results are in agreement with the findings of Trotter and Davies. In general, the two-point limens for the intermediate zones shown in table 10 are practically twice as large as those for normal skin. With nerve regeneration and the consequent reduction of tactile hypesthesia in the intermediate zone the two-point limen of L tends to approximate to the figure secured before denervation. No later two-point judgments were secured from C and W.

TABLE 10.—*Two-Point Limens for Normal Skin and for Intermediate Zones, at a Pressure of 15 Gm.**

	Normal Skin		Day After Denervation	Intermediate Zone	
Subject	Limen, Mm.	Standard Deviation		Limen, Mm.	Standard Deviation
C	36.0	6.56	14	70.8	3.58
L	36.6	3.68	16	78.2	6.80
			133	43.2	4.00
			197	38.0	4.80
W	32.0	5.28	10	52.8	2.20

* The measurements were made longitudinally, on the forearm, within the stamped rectangle.

The inconsistency of two-point judgments on recovering areas was so marked that it seemed impossible to secure meaningful data for computing limens. Therefore no attempt was made to secure systematic two-point judgments in affected areas throughout the course of nerve regeneration. Several factors apparently contributed to the inconsistencies encountered. Perhaps the most important of these was the fact that two areas separated by more than about 1 cm. in a region of nerve regeneration are probably not homologous with respect to subjacent innervation. Also, variations in the distribution of the itching protopathic pains and in spots yielding referred sensations seemed especially to militate against consistency in two-point discrimination in such areas. The judgment "two" was often given for a separation considerably less in magnitude than one which yielded a "one" judgment. Dallenbach failed to observe a systematic increase in percentage of "two" judgments with increasing degrees of separation of the two points, during nerve regeneration. In general it appeared that a process which involved a relation between nerve impulses from two separate areas of skin could not be meaningfully investigated on skin subject to changing conditions of innervation.

13. Dallenbach, K. M.: Nerve Regeneration: Two-Point Limen, Psychol. Bull. **28**:214, 1931.

CONCLUSIONS

We shall first consider the implications of our results for Head's theory of protopathic and epicritic fiber systems in cutaneous nerves. Although this theory has been extensively criticized, it is still regarded by many neurologists and physiologists as the most comprehensive conception yet advanced in explanation of the neural mechanisms underlying cutaneous sensation. Stopford,[14] for example, recently published a volume in which Head's results constitute the factual basis of the analysis of cutaneous fiber systems and in which a modification of Head's theory serves as the theoretical framework. Despite a priori bias in favor of Head's general point of view it is our conclusion that the results presented in the foregoing pages have failed to substantiate his theory on every crucial point. The following experimental facts may be cited in support of this conclusion: 1. The sensory dissociations following denervation do not accord with the requirements of the theory, especially the larger loss of sensitivity to thermal than to touch or pain stimuli and the usual coincidence of anesthesia to touch and to pain. 2. Gradations of sensibility to touch and of two-point discrimination were observed in the intermediate zone, which, according to the theory, should have responded only to prick and to extremes of temperature. 3. The order of return of sensation definitely disagrees with that required by Head's theory and which Head purported to find; sensitivity to touch returned at about the same time and rate as sensitivity to pain and cold and considerably in advance of sensitivity to warmth. 4. On an area retaining sensitivity to light touch no response whatever to cold or warmth stimuli was secured, although Head's theory leads one to expect sensitivity to intermediate grades of temperature in such an area. 5. During nerve regeneration the area just mentioned manifested the protopathic phenomena of abnormal intensification of pain sensation and peripheral reference, showing no inhibition of the activities of the regenerating pain fibers by the intact mechanism of sensitivity to light touch. 6. The course of the qualitative variations in pain (and touch) sensitivity in the intermediate zone was quite different from that observed during nerve regeneration, although Head referred both phenomena to the release of the protopathic system from the inhibition exercised by the epicritic system. The practical abolition of pain in the intermediate zone after the early hyperalgesia and before nerve regeneration is inexplicable on the basis of Head's theory. 7. Variations in the intensity of touch and pain sensations during recovery were contrary to expectations based on Head's hypothesis, as the earliest pains were of normal or subnormal intensity and the increase in the number and intensity of protopathic

14. Stopford, G. S. B.: Sensation and the Sensory Pathway, New York, Longmans, Green & Co., 1930.

pains was accompanied by a decrease of thresholds for touch and an increase in the number of responses to touch. This could not have happened if the return of the epicritic touch fibers had operated to inhibit the protopathic manifestations.

Our results agree substantially with those of Trotter and Davies and of Boring in regard both to the virtual coincidence of the outlines of anesthesia to touch and for pain and to the simultaneity in the return of sensitivity to touch, pain and cold stimuli to anesthetic areas. The systematic dissociation of sensitivity to light touch from pain sensitivity, which constitutes the principal factual basis of Head's theory, was decidedly absent in our three subjects. Head contended, in his comment on the work of Trotter and Davies, that the heavier pressures used by them to display tactile hypesthesia in intermediate and recovering areas stimulated the deep sensibility system, and hence that the sensations produced there were really deep pressure sensations. This criticism is, however, totally irrelevant, as these heavier pressures were not adequate to arouse such deep pressure sensations in areas of cutaneous anesthesia. Furthermore, the touch sensations elicited were similar in quality to those of normal skin and were easily distinguished from the broad, diffuse, nonlocalized deep pressure sensations in areas anesthetic to strictly cutaneous stimuli. The simplest interpretation of these discrepancies between Head's results and those of all later studies is that the light touch stimuli used by Head were inadequate to arouse the hypesthetic contact mechanisms in the intermediate zones and in recovering areas. Head himself observed such touch sensibility early in the course of regeneration, in the form of hair sensibility, but claimed that it was absent in the case of nonhairy skin and that on hairy skin it disappeared after close shaving. Our results contradict these observations.

The sensory dissociations observed by us before and during nerve regeneration point conclusively to the existence of four types of anatomic mechanisms underlying cutaneous sensibility. It is difficult on any other basis to account for the fact that each of the four cutaneous functions was dissociated from the other three at some time during the experiment. Our results do not, of course, throw any light on the character of the diverse mechanisms which seem to be required. The results of recent electrophysiologic studies of nervous impulses in peripheral sensory nerves indicate that these mechanisms may consist of four groups of nerve fibers, each of which mediates a distinct pattern of nervous excitation or action potential wave. The following types of experimental work may be cited in support of this general point of view: (1) the analysis of the complex action potential waves in cutaneous nerves into component waves the forms and rates of propagation of which apparently vary with the size of the fibers constituting the several

groups;[15] (2) studies of the order of abolition of cutaneous processes due to nerve block by anesthetics or pressure;[16] (3) histologic studies of variation in types of fibers in cutaneous nerves, corresponding to variations in the several types of cutaneous sensitivity;[17] (4) studies of the differential masking of cutaneous sensations by stimulation of cutaneous nerves with alternating current.[18] All these investigations agree in allocating touch sensations to the large, rapidly conducting myelinated fibers and pain, cold and warmth sensations to smaller fibers. There is disagreement as to the relative sizes of the fibers mediating sensitivity to pain, cold and warmth. Gasser and Erlanger[16a] and Ranson[17b] allocated cold and warmth sensations to fibers of intermediate size and sensations of pain to the smallest myelinated and unmyelinated fibers. Heinbecker, Bishop and O'Leary[16b] and Thompson and his co-workers[18] held that the smallest of thinly myelinated fibers mediate cold and warmth sensations, while myelinated fibers of intermediate size mediate pain sensations. Our results throw no light on this controversy, although the data on dissociation seems to favor the latter interpretation. The greater loss of thermal sensitivity on denervation may be related to the difficulty of activating the small fibers in the intermediate zone as well as to the relatively greater thinning out of these fibers.

It should be emphasized that the hypothesis of four cutaneous groups of nerve fibers, based on differences in the average diameter of the

15. (*a*) Erlanger, Joseph: The Interpretation of Action Potentials in Cutaneous and Muscle Nerves, Am. J. Physiol. **82**:644, 1927. (*b*) Erlanger, Joseph, and Gasser, H. S.: The Action Potential in Fibers of Slow Conduction in Spinal Roots and Somatic Nerves, ibid. **92**:43, 1930. (*c*) Gasser, H. S., and Erlanger, J.: The Rôle Played by Sizes of the Constituent Fibers of a Nerve Trunk in Determining the Form of Its Action Potential Wave, ibid. **80**:522, 1927. (*d*) Heinbecker, Peter; Bishop, G. H., and O'Leary, James: Fibers in Mixed Nerves and Their Dorsal Roots Responsible for Pain, Proc. Soc. Exper. Biol. & Med. **29**:928, 1932. (*e*) Heinbecker, Peter; Bishop, G. H., and O'Leary, James: Allocation of Function to Specific Fiber Types in Peripheral Nerves, ibid. **30**:304, 1932. (*f*) Hoagland, Hudson: Specific Afferent Impulses and Cutaneous Sensibility, J. Gen. Psychol. **6**:276, 1932.

16. (*a*) Gasser, H. S., and Erlanger, Joseph: The Rôle of Fiber Size in the Establishment of a Nerve Block by Pressure or Cocaine, Am. J. Physiol. **88**:581, 1929. (*b*) Heinbecker, Peter; Bishop, G. H., and O'Leary, James: An Analysis of Sensation in Terms of the Nerve Impulse, Arch. Neurol. & Psychiat. **31**:34 (Jan.) 1934. (*c*) Heinbecker, Bishop and O'Leary.[15e]

17. (*a*) Ranson, S. W.: Cutaneous Sensory Fibers and Sensory Conduction, Arch. Neurol. & Psychiat. **26**:1122 (Dec.) 1931; (*b*) Cutaneous Sensation, Science **78**:395, 1933. (*c*) Ranson, S. W., and Billingsley, P. R.: The Conduction of Painful Afferent Impulses in Spinal Nerves, Am. J. Physiol. **40**:571, 1916.

18. Thompson, I. M., and others: Differential Elevation of Cutaneous Sensory Thresholds by Alternating Currents Applied to a Nerve, Univ. California Publ., Anat. **1**:167, 1934.

fibers, cannot be considered a complete explanation of qualitative differentiation. Adrian [19] has pointed out that the nerve fibers from the skin do not fall sharply into distinct groups based on size; "there are several peaks on the curve showing the number of fibers of each diameter, but that is all that can be said." Recent papers by Ranson and by Gasser indicate that the correlations of the sizes of fibers with sensation and with action potential waves may not be as clearcut as was first assumed.[20] There is apparently considerable variation in the diameters of fibers mediating each of the components of a complex action potential wave, with much overlapping of the several groups. Furthermore, many fibers branch widely on the way to the periphery, the branches being, of course, smaller than the fibers from which they originated, yet no difference in function is conceivable for different parts of the same fiber. Adrian noted also that "fibers in the optic and auditory nerves vary in size and many of them have the same diameter as fibers in the nerves to the skin." The differences in sensation must, therefore, depend to a great extent on differences in their intramedullary courses and central connections.

We have omitted up to this point any reference to the rôle of cutaneous end-organs in sensory nerve activity and in sensation. This omission has been due in part to the lack of conclusive evidence regarding the correlations thus far proposed between specific types of receptors and the several cutaneous qualities. Furthermore, the logic underlying this type of work has seemed to us to be inadequate to explain the complexity of the phenomena. The orthodox theory of cutaneous end-organs is that of von Frey and his collaborators, who advocated the following correlations of receptors with sensory qualities: for touch, the hair follicles and Meissner's corpuscles; for pain, free nerve endings; for cold, the end-bulbs of Krause; for warmth, the cylindric cells discovered by Ruffini. This allocation of functions has been based primarily on correlations of variations in the number of sensitive spots with the distribution of different types of end-organs.[21] Perhaps the most extensive work has been in relation to sensitivity to cold, in which the number and distribution of spots sensitive to cold have been asserted to correspond closely to the number and distribution of end-bulbs of

19. Adrian, E. D.: The Mechanism of Nervous Action, Philadelphia, University of Pennsylvania Press, 1932, p. 58.

20. Ranson, S. W.: Number, Size and Myelination of the Sensory Fibers in Cerebrospinal Nerves. Gasser, H. S.: Conduction in Nerves in Relation to Fiber Types. These papers were read at the fifteenth annual meeting of the Association for Research in Nervous and Mental Disease, New York, Dec. 27, 1934.

21. (*a*) von Frey, Max: Vorlesungen über Physiologie, Berlin, Julius Springer, 1904, pp. 308 to 326. (*b*) Strughold, H., and Karbe, M.: Die Topographie des Kältesinnes auf Cornea und Conjunctiva, Ztschr. f. Biol. **83**:189, 1925.

Krause.[22] This work of the von Frey school and the more recent studies of Bazett and his collaborators [23] seem to be based on the assumption that sensation is the product of the activation of a single receptor and the consequent conduction of impulses along its correlated nerve fiber to the spinal cord and thence to the sensorium. Our results of observations on gradations of sensibility in the intermediate zone contradict such a theory. The much greater loss of cold and warmth sensitivity than of touch of pain sensitivity and especially the loss in our case of all thermal sensibility on skin the primary nerve supply of which was intact, are difficult to explain on the basis of such an oversimplified view. Furthermore, attempts to discover by histologic methods encapsulated end-organs beneath spots sensitive to cold have never met with success.[24] Strughold and Karbe [22b] have, it is true, claimed that by a method of staining the eye in vitro they were able to observe the locations of Krause end-bulbs in the conjunctiva and that after the stain had disappeared they found spots sensitive to cold at the points beneath which such end-bulbs had been seen. The reliability of such results must be questioned, however, since the stain rendered these spots anesthetic at the time the end-bulbs were supposedly visible, and the authors depended on maps of the area in relocating the spots after the stain had disappeared.

Despite the inconclusive character of the evidence for the allocation of different sensory spots to specific receptors, it is our view that differences in end-organs exist. The theory of four types of nerve fibers which we have advocated implies correlated differences in nerve endings. These end-organs, whether special cells or free nerve-endings, probably determine selective excitability as well as variations in the threshold, in rhythms of discharge and in the rate of adaptation. Our objection to the orthodox view of the functions of cutaneous receptors relates mainly to the oversimplified correlation of individual neuro-anatomic units with sensation. Sensation, although apparently a simple discriminative process, probably depends on more complex peripheral excitatory relations than such a theory implies and, further, on complex integrations of patterns of nerve impulses at higher levels of the nervous

22. (*a*) Strughold, H., and Karbe, M.: Die Dichte der Kaltpunkte im Lidspaltenbereiche des Auges, Ztschr. f. Biol. **83**:207, 1925; (*b*) Vitale Färbung des Auges und experimentelle Untersuchung der gefärbten Nervenelemente, ibid. **83**: 297, 1925. (*c*) Strughold and Karbe.[21b]

23. Bazett, H. C.; McGlone, B.; Williams, R. G., and Lufkin, H. M.: Sensation: I. Depth, Distribution and Probable Identification in the Prepuce of Sensory End-Organs Concerned in Sensations of Temperature and Touch; Thermometric Conductivity, Arch. Neurol. & Psychiat. **27**:489 (March) 1932.

24. Dallenbach, K. M.: A Bibliography of the Attempts to Identify the Functional End-Organs of Cold and Warmth, Am. J. Psychol. **41**:344, 1929.

system. Sensation is not to be considered merely an invariable resultant of stimulation of a specialized receptor, followed by conduction of the nerve impulse over a simple conduction pathway to a specific cortical locus.

The concept of patterns of excitation, as opposed to that of the specific energy of a given receptor nerve fiber unit, is the basis of Nafe's quantitative theory of cutaneous sensibility.[25] Nafe, however, considered frequency of discharge to be the essential condition differentiating, for example, touch from pain. Introspective analysis of touch and pain qualities by Nafe's subjects had apparently resulted in the reduction of the difference in quality to a difference in intensity. Nafe correlated these observations with the early results of Adrian and his collaborators,[26] in which a difference in frequency of discharge seemed to be the only physical difference between the action potential waves produced by painful and those produced by nonpainful stimuli. The more analytical studies of action potential waves already cited had not been reported when Nafe formulated his theory. In the light of these studies, as well as of the dissociations observed after denervation, it seems that the patterns of excitation differentiating the four cutaneous qualities depend on different types of mechanisms. It should be emphasized again, however, that this postulation by no means solves the problem of the physiologic processes involved in cutaneous stimulation or that of the character of the activity of the sensorium.

Although the experimental evidence supports a theory of four distinct peripheral mechanisms underlying cutaneous sensibility, the systematically greater loss of cold and warmth sensibility observed by us, in comparison with the loss of sensitivity to touch and pain stimuli, remains unexplained. The outlines for cold and warmth were not coextensive in all the subjects, and especially in W the anesthesia to cold was intermediate in extent between that to warmth and that to touch and pain. Nevertheless both thermal functions manifested considerably greater loss than did the functions for touch or pain. The latter processes showed an unusual degree of association, except in the striking instance of L's triangle. Although no satisfactory theory of the neural or physiologic basis of such phenomena can be formulated as yet, the following theory is proposed as the basis of a tentative organization of the facts and for further discussion and investigation: (1) The areas of distribution of the four types of fibers in a given nerve are as a rule practically coextensive; (2) the sensitivity

25. Nafe, J. P.: A Quantitative Theory of Feeling, J. Gen. Psychol. **2**:199, 1929.

26. Adrian, E. D.: The Basis of Sensation, New York, W. W. Norton & Company, 1928, p. 122.

of an area of skin to a specific stimulus is a function of the mass of fibers of a given type present; (3) the supply of fibers from a given nerve decreases progressively from a maximum in skin nearest the nerve to a minimum at the margin of the receptive area of the nerve; (4) in a region intermediate between two nerves overlapping of fibers occurs, with the result that the elimination of fibers from one nerve produces an anesthetic area beginning where the mass of residual fibers is so reduced that their excitation fails to activate the sensorium; (5) as fibers for cold and warmth are less numerous than those for touch or pain (if the amount of sensitive surface is a reliable criterion) the smaller thermal fibers in an intermediate zone are thinned out relatively more by partial denervation, resulting in more extensive areas of thermal anesthesia, than of areas anesthetic to touch or pain stimuli; (6) the removal of accessory fibers from both sides of an area of intact primary nerve supply may so deplete the mass of fibers for cold and warmth that such functions may disappear entirely (such a case occurred in C's "isolated" area).

According to this theory the loss of cold sensitivity may be expected to be somewhat less than that of warmth sensitivity, since cold sensibility ordinarily is more adequate, as judged by the amount of sensitive surface. This requirement was definitely satisfied in the case of W, and to a lesser degree in that of C or of L. With respect to the phenomena of regeneration, the delay in the return of sensibility to warmth is adequately explained by our theory, although the fact that cold sensibility returns at practically the same time as that to touch and pain constitutes a difficulty. The mechanism for cold may have been expected to lag somewhat behind that for touch or pain during nerve regeneration, if it is assumed that the mass of fibers for cold is less than that of fibers for touch or pain, and consequently that a longer time would be required for their regeneration in sufficient mass to mediate sensation. There was no definite order of precedence in the return of sensitivity, although cold anesthesia disappeared later than that to touch and pain in the cases of C and L—perhaps owing to the greater distal extent of the anesthesia to cold.

Adrian [27] has reported results which seem to contradict our theory that fibers for touch and pain are coextensive in distribution. He observed that at the margin of the receptive field of the cat's ulnar nerve (median side) it was possible to elicit the smaller impulses associated with pain conduction but not the larger impulses typically aroused by light touch stimuli. An alternative interpretation of this failure to secure light touch waves is that the light touch stimuli were subliminal,

27. Adrian,[19] p. 47.

while those for pain were adequate. Our results of studies of the thresholds suggest the necessity of checking carefully the intensity of stimulation at the margin of the receptive field of a nerve, where the mass of fibers may be sharply reduced. The results of Hoagland [15f] in similar studies of cutaneous areas of a frog responding to stimulation with a feather and with acid showed a close correspondence of the outlines of the areas for a given nerve, although the individual spots and the form of the action potential waves differed. The feather which Hoagland used was no doubt a relatively heavy touch stimulus. His results agree with ours in showing that although the general distribution of mechanisms for contact and pain is similar, these mechanisms are, nevertheless, distinct.

A question naturally arises concerning the manner in which the increased intensity of stimulation in the intermediate zone arouses a pattern of nervous energy of supraliminal intensity. It is likely that the higher intensity of stimulation increases the frequency of discharge in the residual fibers and, furthermore, that the effective spatial range of the stimulus is extended, so that fibers are excited which are not affected by stimuli of normal threshold intensity. This theory seems to account both for the changes in the thresholds in intermediate zones and for those manifested in the thresholds in recovering areas.

The abnormal protopathic phenomena of hypersensitivity and reference remain to be explained. These unusual consequences of denervation and nerve regeneration were considered by Head to constitute phenomena impossible of explanation in terms of the traditional theory of receptor specificity. Head explained both the hyperesthesia of the intermediate zone and that of recovering areas in terms of the functioning of the protopathic system uninhibited by the epicritic system. We have shown clearly, however, that the patterns of changes in sensitivity were decidedly different under these two sets of conditions. The same blanket formula of protopathic release could not, therefore, be applied to both types of alteration in sensitivity. In the case of the intermediate zone it seems that some temporary condition enhanced its excitability and that this temporary condition disappeared long before nerve regeneration brought a second stage of hyperalgesia. Trotter and Davies explained the first hyperalgesia on the basis of local irritation of the residual fibers by the products of nerve degeneration. A further possibility is that changes in the cell bodies of degenerating fibers may have affected adjacent cell bodies the fibers of which terminated in the intermediate zone. Either or both of these conditions may have altered the physiologic state of residual fibers so as to have increased their excitability (frequency of discharge). The fact that hypersensitivity was spotty in the intermediate zones suggests a hypothesis of this sort

rather than that of a release of a protopathic mechanism through dissociation. The hypesthetic condition which followed the temporary hyperesthesia in the intermediate zone could be interpreted merely as a reversion to the state observed to be present before the onset of hyperesthesia. Fortunately these hypotheses have the merit of being open to experimental investigation; careful studies of electrical effects produced by stimulation of various parts of the intermediate zone at regular periods after denervation should serve to test their validity.

The changes in sensitivity during nerve regeneration constitute phenomena of a different order from those found in the intermediate zone. With respect to pain, in which the changes were most pronounced, the earliest pains were of subnormal intensity, but with the increase in the mass of fibers as nerve regeneration proceeded, more and more protopathic pains and normal pains of higher grades of intensity were recorded. An especially important feature of the protopathic pains was their excessively unpleasant character and occasional peripheral reference. Trotter and Davies offered no definite explanation of the hypersensitivity occurring during recovery, remarking that "it depends on some condition of the recovering nerve or nerve ending which is only very slowly restored to the normal." More recently Trotter [28] attempted to relate the hyperalgesia of recovery to the lack of adequate insulation of regenerating nerve fibers. These "naked growing fibers" are assumed to be abnormally excitable and in that respect perhaps to approximate the primitive condition of nerve fibers when pain was the principal sensation. The development of insulation he assumes to be the basis of the acquisition of the discriminative aspects of sensation. This theory is rather vague and is difficult to relate to the detailed facts in question. It does not explain why normal pain, which Trotter assumes to be mediated by noninsulated (unmyelinated) fibers, fails to manifest the explosive, protopathic qualities. Furthermore, the theory is inconsistent with the electrophysiologic and histologic work which suggests that pain is mediated, in part at least, by small myelinated fibers. Yet it is not unlikely that the pathologic state of regeneration in nerve fibers conditions the response of the fiber in an important way. In this respect again electrical studies have provided evidence which seems to be especially relevant. When a nerve fiber is injured, as when a nerve is cut through, a depolarized area is formed which results in an "injury" discharge. Adrian [29] has shown that mammalian sensory nerve fibers are especially active after injury and that the impulses manifest a high frequency of discharge. It seems appropriate to assume that injured

28. Trotter, W.: The Insulation of the Nervous System, Lancet **2**:107, 1926.

29. Adrian, E. D.: The Effects of Injury on Mammalian Nerve Fibers, Proc. Roy. Soc. London, s.B **106**:596, 1930.

and regenerating fibers have conditions in common and that the regenerating fiber may well yield a frequency of discharge quite different from that of the normal fiber.

Interesting in this connection are the results of Boeke and Heringa, cited by Woollard,[30] on the histologic examination of an area of skin excised when the protopathic type of sensation was well established. "The result was the discovery of a large number of regenerating nerve fibers and axis cylinders. These showed numerous ramifications, and loops and flattened expansions. . . . Such fibers and endings Boeke and Heringa believed to be capable of functioning and, indeed, to be responsible for Head's protopathic type of sensation. They, however, believed, since some of the fibers showed connections with tactile corpuscles, that the phenomena of protopathic sensation depended not only on a particular type of fiber or ending, but on the imperfect state of all the regenerating fibers." This is substantially our view, except that the correlation with physiologic work on the injury discharge permits one to make a more specific hypothesis in regard to the physiologic basis of protopathic phenomena. Irregularities in the pattern of excitation due to sparseness of nerve fibers in an area, as well as to abnormal frequencies in individual fibers, may affect the thalamus so as to produce the unpleasant affective tone characteristic of the majority of the protopathic reactions. It will be remembered that unpleasantness rather than intensity was the principal characteristic which differentiated protopathic from normal pain. The protopathic touch sensations produced by stroking an affected area have an intermittent, fluttery, unpleasant character in contrast to the smooth, continuous response from normal skin. The combination of inadequate innervation and high frequencies of discharge in such nerve fibers as were functioning might well constitute the peripheral basis of a pattern of nervous excitation which would produce an excessive reaction at the level of the thalamus. Stopford's hypothesis that protopathic intensification of sensation is an instance of thalamic overreaction seems to be valid, although his view (which is also Head's) of the peripheral basis of this phenomenon we have found to be untenable. Furthermore, the hypothesis of thalamic overreaction need not imply that the nervous excitation involved cannot affect the cortex. This conception of the relation of the thalamus and cortex which Stopford proposed seems to be too artificial and abstract. There is no reason to assume that the relation of the cortex to the thalamus is of an "all-or-nothing" character; yet this is precisely the assumption implied in Stopford's con-

30. Woollard, H.: Recent Advances in Anatomy, Philadelphia, P. Blakiston's Son & Co., 1927, pp. 264 and 265.

tention that during the protopathic stage of recovery nerve impulses from affected skin cannot "appeal" to the cortex.[31]

Boring [32] attempted to apply Bernstein's theory of multiple innervation to the variations of threshold and intensity observed after denervation. According to the Boring-Bernstein theory the severance of the primary fibers (i. e., those from the principal nerve to the general area) results in partial loss of function, since the secondary fibers are assumed to be hypesthetic. Mutually inhibitory relations are assumed to exist between primary and secondary fibers of such a nature that when the primary fibers are removed the secondary fibers tend gradually to assume the functions of the former. The secondary fibers are assumed to become more "practiced" with time, and in the absence of inhibition by the primary fibers hypersensitivity may develop in the secondary fibers. When the primary fibers regenerate the secondary fibers are assumed to undergo functional decay, after which normal relations of sensitivity tend to be restored. When both the primary and the secondary fibers are severed, as in completely anesthetic areas, the assumption is that "since the primary fibers are probably in better position to make functional connection than the secondary, they would be the first to become effectively connected; . . . if the secondary fibers did not return rapidly to function, the *p*-excitation might rise above normal." [33] Various other applications of the assumed relations of these two classes of fibers are made to account for other observed phenomena. In general this theory, like Head's, is untenable because it applies a general blanket theory to phenomena which appear to be diversely conditioned. The literal translation of all possible alterations in threshold and intensity resulting from denervation into hypothetical relations of two sets of fibers with such differential properties of excitability and rate of regeneration seems, on the basis of our results, oversimplified and inadequate. The theory fails, for example, to account for the second stage of hypersensitivity which we observed in the intermediate zone. The mass innervation theory already outlined is based on none of these peculiar assumptions about the functional aberrations of individual fibers and, furthermore, is stated in terms which imply the possibility of experimental investigation.

Peripheral reference, which we found to occur for all four modes of sensation, is most simply explained on the basis of abnormal fiber connections. Nerve fibers innervating a spot yielding referred sensation may be assumed to have terminated formerly in skin distal to the area

31. Stopford,[14] p. 116.

32. Boring,[3] p. 86.

33. Boring,[3] p. 91. Boring used the term *p*-excitation to refer to excitation of the primary fibers.

in question. Stimulation of these fibers would arouse perceptual motor habits associated with stimulation of the former terminus of the fibers. In this connection it should be noted that Stopford's hypothesis of special localization fibers is unnecessary and probably invalid. The obvious objection to such a theory is that localization is not a sensation sui generis; the sensations localized are those of touch, pain, cold and warmth, depending on the stimulus. Although peripheral differentiation is undoubtedly an important condition of capacity for localization, it seems probable that cortical integration of cutaneous with kinesthetic impulses is the crucial factor in the process. Disturbance of the hitherto stable conditions on which localization depended would naturally produce erroneous responses which could be corrected only through practice or through the more complete regeneration of fibers which formerly innervated the area.

SUMMARY

The injection of alcohol into various branches of the medial and lateral antebrachial cutaneous nerves in the left forearm of three subjects resulted in the production of five anesthetic areas.

The principal pattern of sensory dissociation revealed by careful outlining of these areas was that of a much more extensive loss of thermal sensitivity than of touch or pain sensitivity. The anesthesia to cold was somewhat less extensive than that to warmth stimuli; the outlines for touch and pain usually manifested close conformity.

One striking instance of dissociation of touch sensitivity from pain sensitivity was observed in a large triangular area which retained practically normal sensibility to touch but lacked sensibility to pain stimuli.

Sensibility to pain, touch and cold stimuli began to return to affected areas at about the same time and advanced distalward at approximately the same rate; the return of warmth sensibility was considerably delayed. Individual differences in rates of restoration of these functions were observed in the three subjects.

The thresholds for both pain and touch were found to increase gradually on going from normal skin to the border of an anesthetic area. The thresholds for touch in such intermediate zones returned gradually to a normal level, apparently with nerve regeneration. The thresholds for pain, however, showed a remarkable increase after a few weeks, even on skin which possessed normal acuity shortly after the injection into the nerve. This phenomenon was especially marked in areas deprived of accessory innervation from both sides. Pain sensibility in such regions was almost abolished for more than a year.

The thresholds for touch and pain in recovering areas were high at first and gradually returned to a normal level as nerve regeneration

proceeded. Touch sensitivity regained normal acuity, in terms of the threshold, considerably in advance of pain sensitivity. Hypersensitivity to prick, in terms of the threshold, developed at approximately the end of a year and was still present in most of the affected areas three years after denervation.

In terms of intensity of sensation the following patterns of changes in sensitivity were observed: 1. In the intermediate zones touch sensation showed hypesthesia, hyperesthesia, a normal level, and pain sensation showed hyperalgesia, hypalgesia, hyperalgesia, a normal level. 2. In recovering areas (i. e., formerly anesthetic areas) touch sensation showed hypesthesia, hyperesthesia, a normal level; pain sensation showed hypalgesia, hyperalgesia, a return toward a normal level; cold sensation showed hypesthesia, hyperesthesia, a normal level; for warmth sensation hypesthesia existed throughout recovery, except for a period in which warmth stimuli produced pain. These generalizations refer to sensitivity to punctiform stimuli. The affected areas have never recovered normal sensitivity from the point of view of the character of the effects of areal stimulation.

The return of pain sensation to the triangle which retained sensitivity to touch was characterized by the same type of qualitative and quantitative changes as were observed for other analgesic areas. The presence of normal sensitivity to contact failed to inhibit the manifestation of protopathic pain in this area during regeneration.

The capacity to localize a stimulus of 15 Gm. was definitely impaired by cutaneous denervation, despite the operation of auxiliary factors which might have tended to lessen the error of localization as compared with that for normal skin.

Two-point discrimination was absent from skin anesthetic to touch stimuli, with maximum separation of the points of the esthesiometer used (80 mm.). The two-point limen in areas of deep tactile hypesthesia was practically twice as great as that for normal skin.

The results of the study do not substantiate Head's hypothesis of protopathic and epicritic systems of fibers in cutaneous nerves. Neither the phenomena of sensory dissociation nor the patterns of changes in sensitivity occurring in intermediate and in recovering areas can be explained by this theory.

The sensory dissociations observed point conclusively to the existence of four types of anatomic mechanisms underlying cutaneous sensibility. The most plausible theory seems to be that these mechanisms consist of four groups of nerve fibers, each of which produces a distinct pattern of nervous excitation or action potential wave. The diameter of the fibers is probably an important basis of differentiation of the several groups. This theory has received strong support from recent studies

of electrical changes in nerves and from studies of the effects of cutaneous anesthetics showing selective abolition of sensations, apparently in relation to characteristic groups of fibers.

The measurements of the thresholds indicate that the threshold for sensation, in contrast to the threshold of peripheral nerve fibers, varies somewhat directly with the mass of nerve fibers present in a given area of skin. Toward the margin of the receptive field of a nerve (the intermediate zone) and in recovering areas in the early stages of nerve regeneration innervation is no doubt relatively sparse, and our results showed that under such conditions the thresholds were high. The more intense stimulation necessary is assumed to have evoked a higher frequency of discharge in the fibers that were affected and perhaps also to have affected fibers relatively remote from the point stimulated.

The larger areas of thermal anesthesia, as compared with the areas of anesthesia to touch or pain, is explained in terms of the same principle of mass innervation. Partial denervation such as occurs in the intermediate zone would result in relatively greater thinning out of fibers for cold and warmth, since they are presumably much less numerous, with the result that the excitation of residual thermal fibers at the outer margin of the receptive field would be inadequate to arouse the sensorium. The slightly less extensive loss of cold sensitivity as compared with that of warmth sensitivity is correlated with the greater surface area responsive to cold stimuli and an assumed greater mass of cold fibers. The delay in return of warmth sensibility can be explained on the same principle; a longer time would be necessary for the fewer fibers for warmth to return in sufficient number to yield a nervous discharge adequate to activate the sensorium. The fact that sensitivity to cold stimuli returns as fast as that to touch or pain stimuli does not, however, conform to expectations based on this theory.

The peculiar protopathic overreaction observed in the intermediate zone and in affected areas during nerve regeneration is held to be differently conditioned in the two instances. Studies of action potential waves indicated that the intensity of sensation is correlated with the frequency of nerve impulses, other things being equal. The temporary hyperesthesia of the intermediate zone can be explained in terms of an increased excitability of the residual fibers, caused either by local effects (chemical or physical) of nerve degeneration or by changes in the spinal ganglion accompanying the axon reaction in affected cell bodies. The hyperesthesia occurring during regeneration could be due to an increased frequency of discharge in regenerating fibers, analogous to the injury discharge described by Adrian. The excessively unpleasant character of the pain thus induced is held to be an instance of thalamic over-

reaction caused by the abnormal pattern of excitation occurring in the relatively few fibers discharging at high frequencies.

Abnormal localization (peripheral reference) seems to be due to abnormal terminations of fibers; fibers originally ending at more distal points find their way to the skin before reaching these points. Localization is held to be an acquired function and is not believed to depend on special localization fibers.

CEREBRAL BIRTH CONDITIONS, WITH SPECIAL REFERENCE TO MYELOGENY

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The question of the cause or causes of feeblemindedness is no nearer solution today than thirty years ago, despite the enormous amount of investigation that has been carried out pathologically and experimentally. The multiplicity of the clinical syndromes in the group of mental deficiencies attests to the variations that may be expected in undertaking a study of these conditions. After eliminating all accidental mental deficiencies due to infection or injury that robs normally born children of their intelligence, we may divide the remainder for the sake of convenience into two general classes: (1) feeblemindedness with no neurologic defects and (2) feeblemindedness with neurologic defects. There are also patients who show endocrine dysfunction, but their conditions may as a rule be classified in one of the two groups just mentioned. The entire group of mental deficiencies may be more scientifically classified from a clinical standpoint, as advocated by Potter,[1] under a number of headings, including prenatal influences, infections, trauma, convulsive disorders, disturbances of metabolism, new growths and undetermined causes. Such a classification appears more complicated than is necessary for our purpose. We are, however, fully in accord with Potter in his belief that the adoption of a clinical classification will do much to stimulate investigation of the etiologic causes. Each patient should, of course, still be classified psychologically as an aid in determining his capabilities and potentialities for education and training.

MATERIAL

A neurologic survey of the patients in the Philadelphia Institution for Feeble Minded was made in an effort to determine the percentage and type of neurologic manifestations that one is likely to encounter in a group of this sort and, if possible, to correlate to some extent the degree and type of physical and neurologic defects with the intellectual level. The data give a general cross-section of the clinical aspects of the problem of feeblemindedness and indicate the type of cases likely to be encountered in a group of this size. Three hundred and fifty patients in all were examined.

1. Potter, H. W.: A Clinical Consideration of Mental Deficiency, Psychiatric Quart. **7**:195 (April) 1933.

Eighty-two and six-tenths per cent of the patients examined have an intelligence quotient below 50, for the obvious reason that no lower age limit or minimum mental level is required for admission to the institution, and many patients are very young at the time of admission. Because of the type of patients admitted, the percentage of those showing very low levels of intelligence and organic neurologic defects is naturally greater than is ordinarily found in institutions for the feebleminded which maintain a somewhat rigid classification from both the physical and the intellectual standpoint.

NEUROLOGICALLY NORMAL GROUP

Slightly more than 50 per cent of these patients can be considered as being neurologically "normal." By this we mean that on examination they manifested no signs or symptoms of involvement of the pyramidal

TABLE 1.—*Psychologic Classification of Entire Group*

	Number	Percentage
Morons	61	17.4
Imbeciles	130	37.2
Idiots	159	45.4
Total	350	100.0

TABLE 2.—*Psychologic Classification of Neurologically Normal Patients*

	Number	Percentage of Group	Percentage of All Patients
Morons	40	22.3	11.4
Imbeciles	75	42.0	21.4
Idiots	64	35.7	18.3
Total	179	100.0	51.1

or extrapyramidal tracts or of sensory impairment. Ocular imbalance, visual impairment and other disorders, when occurring as isolated phenomena, are not considered as positive neurologic findings unless accompanied by evidence of involvement of motor tracts.

Fifteen patients with mongolism who are either low grade imbeciles or idiots are included in this group, which tends to lower the general mental level of the group. In spite of this fact it may be seen at a glance that the group has a high percentage of children with intelligence of higher grade as compared with the total number of morons and imbeciles in the institution.

Case 1 illustrates the neurologically normal group as a whole.

CASE 1.—*A familial type of mental defective with the level of intelligence of a high grade imbecile, who is well developed, well nourished and neurologically normal.*

B. G., a white girl, aged 17, was admitted on Oct. 22, 1925. She has an intelligence quotient of 47. Both the father and the mother are irresponsible morons, and the family had been receiving aid from various welfare organizations

for the past fifteen years. There are 5 siblings; the oldest, a girl, was formerly a patient in this institution and was classified as on the borderline of mental deficiency. She is now married and seems to be adjusting well. She is the most enterprising member of the family. A brother, aged 13, is mentally defective and has a congenital malformation of the hands. A sister, aged 10, has progressed only as far as the third grade in the public schools. The youngest sibling, a boy, aged 8 years, is a patient in the Philadelphia Institution for the Feeble Minded. He is a low grade imbecile.

Prior to admission, B. G. had been neglected and had received no training. The condition of the family was brought to the attention of the Pennsylvania Society to Protect Children from Cruelty, which resulted in the commitment of the patient to this institution. At the time of admission her intelligence quotient was 71. She has deteriorated since then. She has second grade academic ability, but her memory is poor and her judgment is meager. She is always well behaved and a willing worker. Physically, she is developed proportionally and essentially normal but is somewhat small for her age.

TABLE 3.—*Psychologic Classification of Neurologically Normal Patients with Convulsive Seizures*

	Number	Percentage of Group	Percentage of Neurologically Normal Patients
Morons	6	20.7	3.3
Imbeciles	11	37.9	6.1
Idiots	12	41.4	6.7
Total	29	100.0	16.1

Although epilepsy is not uncommon among neurologically normal patients, it is observed less frequently than in patients showing definite neurologic involvement. The psychologic classification of this group, analyzed in table 3, is much the same as for the group as a whole. It appears that epilepsy among neurologically normal patients is no more likely to occur in the lower grade mentally defective child than in the moron, although deterioration is more likely to occur in patients having convulsive seizures.

The patients belonging in this group as a rule differ little from the patient in case 1, except for the additional factor of epilepsy with its sequelae. However, certain patients in this group present a more difficult behavior problem, and a number show periods of excitement which are related to the convulsive episodes, as exemplified in case 2.

CASE 2.—*A well developed, well nourished low grade moron with frequent convulsive seizures, who presents a behavior problem.*

D. Z., a white boy, aged 8, who was admitted on May 12, 1932, has an intelligence quotient of 55. The family history reveals no neuropathic taint except that a paternal uncle had convulsive seizures. There are 5 siblings, all living and well. The mother's pregnancy was uneventful, and birth was normal. The patient was bottle fed. He sat at the usual age; dentition was normal. He walked and began to talk at the age of 1 year. Whooping cough at the age of 2 months was

TABLE 4.—*Neurologically Normal Patients—Composite Summary*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Physical Defects and Other Conditions
1	W. A.	M	8	2	24	24	No history	Macrocephaly
2	P. B.	M	15	1	21	19	Normal	
3	G. B.	M	13	2	?	51	No history	Macrocephaly
4	M. B.	M	8	5	31	31	Normal	Convulsive seizures
5	E. B.	M	14	2	27	54	Breech delivery	
6	H. B.	M	13	6	37	29	Cyanotic at birth	Convulsive seizures
7	C. B.	M	12	5	40	72	No history	
8	R. B.	M	9	2	25	46	Normal	
9	C. B.	M	10	1	18	31	No history	
10	M. B.	M	17	1	16	15	Difficult	
11	E. B.	M	6	4	23	14	No history	
12	R. B.	M	17	2	26	14	Normal	
13	E. B.	M	17	1	18	21	No history	Albino Negro
14	I. B.	M	6	1	26	53	No history	Mongolism; convulsive seizures
15	W. B.	M	15	1	24	53	Normal	
16	W. C.	M	7	1	26	37	No history	Muscular hypotonicity
17	W. C.	M	14	2	29	12	No history	Oxycephaly
18	M. C.	M	7	2	23	3	No history	Cranial asymmetry
19	A. C.	M	10	1	25	25	No history	Mongolism
20	J. C.	M	18	2	?	48	No history	Oxycephaly
21	R. C.	M	15	1	18	15	No history	
22	F. C.	M	13	8	44	48	Normal	
23	C. C.	M	9	3	27	30	No history	
24	J. C.	M	18	4	30	16	No history	
25	W. C.	M	14	3	28	12	No history	
26	W. D.	M	12	2	27	56	Premature	Hyperactive
27	S. D.	M	16	3	26	47	Normal	
28	S. D.	M	8	2	31	23	Normal	Convulsive seizures
29	L. D.	M	11	1	25	37	Difficult	Hyperactive
30	S. D.	M	7	2	21	20	No history	
31	B. F.	M	5	5	31	32	Difficult	Cleft palate
32	W. F.	M	10	2	34	30	Normal	Macrocephaly; hyperactive
33	L. F.	M	15	2	24	74	Normal	
34	M. G.	M	18	3	26	37	Normal	
35	T. G.	M	14	4	35	20	Normal	Mongolism
36	F. G.	M	12	1	23	15	Normal	
37	I. G.	M	12	5	34	19	Normal	Macrocephaly; epileptic equivalents
38	L. G.	M	7	1	23	34	Normal	Hyperactive
39	I. G.	M	9	2	27	23	Difficult	Congenital cataracts
40	A. G.	M	11	1	?	31	No history	
41	L. G.	M	7	2	?	32	No history	Convulsive seizures
42	H. G.	M	10	3	24	13	Normal	Cranial asymmetry; atrophic right eye; corneal opacity in left eye; blind
43	R. G.	M	17	3	?	58	No history	
44	M. G.	M	15	2	32	46	Influenza	Convulsive seizures
45	W. G.	M	18	1	?	52	No history	
46	R. G.	M	14	1	25	49	No history	Muscular hypotonicity
47	E. G.	M	16	1	18	55	Normal	
48	L. G.	M	8	5	28	40	No history	Cataract of right eye
49	J. H.	M	9	1	32	47	Normal	Hyperactive
50	T. H.	M	15	3	41	60	No history	
51	L. H.	M	11	5	33	28	Normal	
52	A. H.	M	17	1	16	70	No history	
53	L. H.	M	13	5	36	65	No history	
54	R. H.	M	8	1	29	25	No history	
55	J. J.	M	13	2	33	42	No history	
56	F. J.	M	11	3	23	31	Normal	
57	R. J.	M	17	1	?	32	No history	
58	E. K.	M	10	1	31	11	Normal	Cranial asymmetry; blind; mongolism; convulsive seizures
59	G. K.	M	19	1	27	11	Difficult	Mongolism
60	T. K.	M	15	2	20	67	No history	
61	B. K.	M	11	1	19	8	Normal	Mongolism
62	A. K.	M	14	4	29	23	No history	
63	G. K.	M	13	4	27	40	Premature	
64	D. K.	M	5	3	23	43	No history	
65	C. L.	M	6	2	43	24	Difficult	Muscular hypotonicity
66	I. L.	M	14	1	19	20	No history	Small, round head; hyperactive
67	A. L.	M	13	7	31	19	Difficult	Mongolism
68	B. L.	M	10	8	36	17	Attempted abortion; normal	Mongolism
69	L. M.	M	8	6	30	34	Normal	Convulsive seizures
70	J. M.	M	5	2	27	8	No history	Mongolism; congenital heart disease; dislocated patellae

TABLE 4.—*Neurologically Normal Patients—Composite Summary—Continued*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Physical Defects and Other Conditions
71	A. M.	M	14	2	40	14	Difficult	Mongolism
72	P. M.	M	13	4	24	40	Normal	Positive Wassermann reaction
73	J. M.	M	4	1	?	18	No history	Oxycephaly
74	F. M.	M	12	1	?	71	No history	
75	G. M.	M	16	1	?	82	No history	
76	R. M.	M	6	5	40	51	Breech delivery	Convulsive seizures
77	W. M.	M	11	3	?	56	Child cyanotic	
78	G. M.	M	19	1	18	41	Difficult	Psychosis
79	N. O.	M	15	1	37	26	No history	
80	N. P.	M	11	3	33	25	No history	
81	C. P.	M	10	1	30	30	No history	Mongolism
82	W. P.	M	5	7	31	23	No history	
83	J. P.	M	11	8	29	53	No history	Convulsive seizures
84	H. R.	M	13	3	29	45	No history	
85	J. R.	M	13	1	20	20	No history	Positive Wassermann reaction
86	E. R.	M	11	2	26	51	Normal	
87	E. R.	M	9	1	19	5	Premature, difficult	Macrocephaly
88	J. S.	M	18	4	36	12	No history	Convulsive seizures
89	A. S.	M	18	5	53	27	No history	Mongolism
90	E. S.	M	13	1	37	59	Normal	Klippel-Fell syndrome
91	W. S.	M	14	1	26	18	No history	Hyperactive
92	J. S.	M	18	2	24	57	No history	
93	P. S.	M	20	5	39	14	No history	Mongolism
94	J. S.	M	14	2	19	32	No history	Convulsive seizures
95	A. S.	M	7	1	19	22	Difficult	Convulsive seizures
96	J. S.	M	11	4	36	27	No history	
97	J. S.	M	19	2	19	50	No history	Blind
98	R. S.	M	5	2	17	26	Mother had chorea during pregnancy	Hyperactive (brother of V. S.)
99	V. S.	M	7	1	16	47	Mother had chorea during pregnancy	Enlarged thymus (brother of R. S.)
100	A. S.	M	15	2	20	50	No history	
101	D. S.	M	7	2	32	21	Normal	Convulsive seizures
102	C. T.	M	12	1	25	42	No history	
103	R. T.	M	4	1	18	29	No history	Mannerisms
104	W. T.	M	12	2	?	32	Normal	
105	A. T.	M	12	2	26	18	No history	Cretin
106	J. T.	M	8	2	27	21	No history	
107	J. U.	M	12	3	33	32	Premature	
108	C. V.	M	10	5	39	18	Normal	Convulsive seizures
109	P. V.	M	11	5	29	35	Normal	Macrocephaly
110	C. W.	M	15	3	29	61	No history	
111	C. W.	M	10	4	?	24	No history	Macrocephaly; achondroplasia (Twins)
112	C. W.	M	10	4	?	15	No history	Macrocephaly; Hutchinson's teeth; achondroplasia (Twins)
113	H. W.	M	12	1	32	30	Normal	
114	D. Z.	M	8	4	24	55	Normal	Convulsive seizures
115	E. A.	F	11	1	20	30	Premature, difficult	Mongolism
116	A. A.	F	7	1	?	51	No history	
117	S. B.	F	16	1	25	48	Normal	Psychotic episodes
118	E. B.	F	8	4	40	15	No history	Mongolism
119	E. C.	F	8	2	21	19	Normal	
120	H. C.	F	12	5	31	9	Difficult	Convulsive seizures
121	L. C.	F	6	2	25	44	Normal	
122	S. C.	F	9	5	41	33	Normal	
123	T. C.	F	10	1	31	33	No history	
124	P. C.	F	17	2	28	56	No history	Positive Wassermann reaction
125	C. C.	F	10	3	32	35	No history	
126	L. C.	F	7	2	26	49	Normal	Congenital dislocation of hip
127	J. D.	F	19	2	?	39	No history	
128	G. D.	F	8	5	29	10	No history	
129	E. D.	F	6	1	23	32	Normal	Hypotonicity
130	M. D.	F	6	3	30	16	No history	
131	E. E.	F	9	3	39	44	Normal	
132	M. F.	F	15	1	20	18	No history	Hyperactive
133	L. F.	F	13	2	21	38	No history	Mongolism
134	R. F.	F	3	1	47	25	No history	Mongolism
135	Y. F.	F	15	2	30	52	No history	
136	I. F.	F	12	3	36	24	Normal	Cranial asymmetry; mongolism
137	M. G.	F	10	1	24	46	No history	Convulsive seizures
138	L. G.	F	37	?	?	59	No history	

TABLE 4.—*Neurologically Normal Patients—Composite Summary—Continued*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Physical Defects and Other Conditions
139	E. G.	F	14	1	18	71	Normal	Convulsive seizures
140	B. G.	F	17	2	19	47	No history	
141	S. H.	F	6	6	?	20	Normal	
142	M. H.	F	14	1	18	28	No history	
143	W. H.	F	10	1	24	56	No history	
144	H. H.	F	6	5	25	18	No history	
145	A. H.	F	16	3	?	8	No history	Decompression operation; convulsive seizures
146	N. J.	F	11	3	37	60	Difficult	Tuberculosis of hip
147	M. J.	F	15	1	23	14	Difficult	Convulsive seizures; periods of excitement
148	R. J.	F	12	1	?	44	No history	
149	R. K.	F	7	1	30	19	No history	Macrocephaly; corneal opacity and anterior staphyloma of right eye; polydactylism; absence of soft palate
150	H. L.	F	14	2	26	32	No history	Cranial asymmetry
151	L. L.	F	17	2	23	41	Normal	Saber-shaped tibia; convulsive seizures
152	E. M.	F	10	1	?	65	No history	
153	D. M.	F	19	1	?	58	No history	Positive Wassermann reaction
154	E. M.	F	8	3	?	47	Normal	Convulsive seizures
155	M. M.	F	16	1	30	48	No history	
156	D. M.	F	16	1	38	47	No history	
157	M. M.	F	9	1	19	40	No history	Convulsive seizures
158	H. M.	F	11	5	40	22	No history	Congenital cataracts; mannerisms; convulsive seizures
159	R. O.	F	9	1	17	35	No history	
160	R. O.	F	8	8	37	15	Difficult	Webbed toes; aged appearance; translucent skin
161	L. P.	F	7	1	25	13	Difficult	
162	V. P.	F	9	1	22	44	No history	
163	M. P.	F	20	1	?	38	No history	
164	E. R.	F	14	1	18	38	No history	Congenital cataracts; convulsive seizures
165	L. R.	F	16	4	39	19	Mother psychotic	Mongolism; blind
166	A. R.	F	19	2	?	28	Normal	
167	M. S.	F	10	2	26	28	Normal	
168	R. S.	F	7	1	18	20	Normal	Hypotonicity
169	V. S.	F	10	1	20	26	Normal	
170	M. S.	F	14	2	27	57	Difficult	Congenital deformity of right ankle; convulsive seizures
171	L. S.	F	10	4	25	64	No history	
172	M. T.	F	19	1	33	43	No history	
173	D. T.	F	15	2	27	31	Normal	
174	I. T.	F	5	2	?	17	No history	Saber-shaped tibia
175	S. U.	F	40	?	?	23	No history	
176	P. W.	F	12	2	23	14	Normal	Convulsive seizures
177	I. W.	F	18	1	?	68	No history	
178	L. N.	F	17	1	18	13	Normal	Left eye enucleated; congenital cataract in right eye
179	M. O.	F	17	1	?	40	Difficult	Glandular dysfunction

the only disease of childhood that he had. The first convulsive seizure occurred at the age of 9 months, and attacks became increasingly more frequent until the time of hospitalization. At home he presented a difficult behavior problem; he was irritable, assaultive and destructive, especially just before an attack. There has been little change in the patient's condition since admission, although he is more cooperative and has had fewer convulsive seizures. He has an average of eight or ten grand mal attacks monthly. He has good analytic discrimination, control and coordination. He is trainable to a moderate degree, but is practically uneducable. He seems unable to absorb more than a few of the fundamentals of reading and arithmetic. Physically, he is well developed and well nourished. There are no physical or neurologic defects. Laboratory studies give entirely negative results.

Case 2 might be considered one of a type of mental deficiency due to epilepsy, but as the convulsive seizures began at a very early age we cannot be certain that the patient ever had normal intelligence. It is possible that the case is one of familial mental deficiency complicated by a convulsive disorder.

So-called stigmas of degeneration have been noted in numerous patients but have been given no particular attention. Developmental cranial anomalies of slight degree have frequently been observed, but they cannot be considered as being within the scope of this article. It should be mentioned that only a few of our patients can be considered as having an entirely normal physical development.

GROUP WITH POSITIVE NEUROLOGIC FINDINGS

Slightly less than 50 per cent of the patients examined manifested pyramidal or extrapyramidal syndromes. These are designated as patients with positive neurologic findings. Particular interest centers

TABLE 5.—*Psychologic Classification of Patients with Positive Neurologic Findings*

	Number	Percentage of Group	Percentage of All Patients
Morons	21	12.3	6.0
Imbeciles	55	32.2	15.7
Idiots	95	55.5	27.1
Total	171	100.0	48.8

in this group, whose conditions have been classified under several different headings, 14 being listed under more than one heading.

An interesting comparison may be made between the entire group with positive neurologic findings, as classified according to the psychologic levels, and the neurologically normal patients.

It is interesting to note that the greatest number of patients fall into the idiot group, and there has been found to be a considerable relationship between the degree of neurologic involvement and the intellectual level. This is especially true with reference to patients with congenital spastic diplegia; in only two instances were children with a marked degree of spasticity found to have an intelligence quotient above 50. This we consider of interest in view of statements in the literature. Tredgold [2] stated in relation to lesions of the brain causing mental defect:

> It is sometimes stated that if paralysis results from one of these lesions, some degree of mental defect will inevitably result. This is certainly not so. I have seen a number of instances in which there was a mono-, hemi-, or even diplegia,

2. Tredgold, A. F.: Mental Deficiency, ed. 5, New York, William Wood & Company, 1929, p. 245.

without any intellectual impairment whatever; indeed, in some of these cases the mental capacity has been above the average.

Although such cases exist without doubt, they must constitute an insignificant percentage of cases of patients suffering from congenital spastic palsies, even if those thought to have been caused by trauma at birth are considered in this category.

TABLE 6.—*Psychologic Classification of Patients with Positive Neurologic Findings with Convulsive Seizures*

	Number	Percentage of Group	Percentage of Positive Neurologic Findings
Morons	4	6.5	2.3
Imbeciles	15	24.2	8.8
Idiots	43	69.3	25.1
Total	62	100.0	36.2

TABLE 7.—*Psychologic Classification of Patients with Neurologic Manifestations Due to Lesions Apparently Congenital in Origin*

	Number	Percentage of Group	Percentage of Positive Neurologic Findings	Percentage of All Patients
Morons	18	11.6	10.5	5.1
Imbeciles	47	30.1	27.5	13.4
Idiots	91	58.3	53.3	26.0
Total	156	100.0	91.3	44.5

TABLE 8.—*Psychologic Classification of Patients with Neurologic Manifestations Due to Postnatal Causes*

	Number	Percentage of Group	Percentage of Positive Neurologic Findings	Percentage of All Patients
Morons	3	20.0	1.7	0.9
Imbeciles	8	53.3	4.6	2.2
Idiots	4	26.7	2.3	1.1
Total	15	100.0	8.6	4.2

Of the patients with neurologic conditions, 36.1 per cent have convulsive seizures, and more than two thirds of these have an intelligence quotient below 25. These figures tend to bear out Tredgold's [2] contention that the presence of epilepsy is a more serious augury than paralysis.

One hundred and fifty-six patients with neurologic manifestations have lesions which are apparently congenital. This group includes a number of patients whose lesions may have resulted from injuries sustained at birth and also patients for whom a history was wanting, inconclusive or unreliable but who showed nothing to suggest a postnatal cause for the condition.

Fifteen patients have lesions that are apparently postnatal in origin.

No definite conclusion can be drawn from the figures in tables 7 and 8 as to any difference in the mental level to be expected in the two groups, but it would be expected that patients who enter life

TABLE 9.—*Patients with Neurologic Conditions of Postnatal Origin—Composite Summary*

Case and Name	Sex, and Age in Years	Character of Birth	I. Q.	Trauma or Disease	Neurologic Condition	Comment
1 J. F.	M 15	Normal	41	Injury to head at age of 3, followed by convulsive seizures to date	Hyperreflexia, positive Babinski sign and ankle clonus; muscular incoordination	Decompression operation following injury
2 J. G.	M 10	No history	33	Anterior poliomyelitis	Flaccid paraplegia	
3 C. G.	M 13	Normal	8	Extensive burn at age of 3½, followed by convulsive seizures	Advanced spastic diplegia	Spasticity progressing; I. Q. was 44 in 1927
4 G. M.	M 19	Normal	43	History of physical abuse	Parkinsonism	No history of encephalitis; sister feebleminded, died in status epilepticus
5 W. O.	M 19	No history	19	Epilepsy	Cranial and facial asymmetry; atypical athetoid movements of face, trunk and extremities	Normal until onset of convulsive seizures
6 A. T.	M 17	Normal	47	Anterior poliomyelitis	Flaccid paralysis of left leg	
7 W. W.	M 12	Normal	43	Meningitis at 12 months	Hydrocephaly (spastic quadriplegia)	Ventriculography; more than a liter of fluid removed
8 M. F.	F 16	No history	57	Anterior poliomyelitis	Flaccid paraplegia	
9 R. G.	F 13	No history	58	Anterior poliomyelitis	Flaccid paraplegia	Mentally defective prior to poliomyelitis
10 S. H.	F 6	Labor was difficult	38	Epilepsy	Right hemiplegia	Paralysis developed 2 months before examination following convulsive seizures
11 M. E.	F 17	No history	45	Febrile illness at age of 4	Right spastic hemiparesis; athetosis of right hand	
12 D. L.	F 11	Normal	30	Injury to head at 2 months	Hydrocephaly; spastic diplegia; convulsive seizures	
13 H. M.	F 11	Normal	16	Measles with encephalitis	Left hemiparesis; convulsive seizures	
14 J. S.	F 14	No history	51	.....	Parkinsonism	No history of encephalitis
15 E. R.	F 5	Normal	12	Epilepsy	Spastic hemiparesis	

presumably fully equipped to carry on the struggle and who subsequently suffer from some illness or injury would be likely to show more circumscribed lesions, such as hemiplegia or monoplegia and less complete mental retardation. Our figures seem to bear this out to a certain extent.

In none of the cases listed in table 9 can we be absolutely certain that the mentality of the patient prior to the illness or injury was entirely normal. Two of the patients have especially interesting histories.

CASE 3.—*A boy with marked internal hydrocephalus with hemiparesis and epilepsy following meningitis at the age of 12 months, resulting in physical helplessness and imbecility.*

W. W., a colored boy, aged 12, with an intelligence quotient of 43, was admitted on Oct. 7, 1931. The family history revealed no neuropathic taint. The mother's gestation and labor were normal. The child's physical development was normal during the first year of life. At the age of 12 months he had some form of meningitis, which was followed by epilepsy and hydrocephalus. He is said to have learned to talk at the age of 9 months, but he did not walk until 3 years of age. Little is known concerning his condition between the age of 1 year and the time that he was admitted. On July 31 he was admitted to the neurosurgical service of the Graduate Hospital of the University of Pennsylvania for study. The outstanding physical findings at that time were hydrocephalus, hemiplegia on the right, marked lateral nystagmus and mental retardation. On August 11 an encephalogram was taken. The spinal fluid pressure was 46 mm. of mercury; 98 cc. of fluid was withdrawn and the same amount of air injected. The roentgenologist reported: "The anteroposterior view shows only a slight amount of air in the subdural space. The amount of air injected was insufficient to outline the various anatomic portions of the skull. It is therefore impossible to come to any conclusions. There is marked evidence of internal pressure. The markings are more prominent on the left than on the right; however, the right side appears to be somewhat larger. The pituitary fossa is enlarged. The clinoid processes appear normal. I believe this to be compensatory with the enlargement of the skull." The patient had a moderate febrile reaction following this procedure, which lasted for about forty-eight hours. He remained drowsy for several days and then improved rapidly. On August 25 a ventriculogram was made, and about 1,000 cc. of fluid was removed through the needle on the left side. The child was then taken to the x-ray department. During the next hour the ventricles were tapped four times, and a gush of air escaped on each occasion. Following this procedure the temperature began to rise, and the pulse rate became more rapid. The child appeared drowsy, but this was thought to be due to the amount of amytal administered. That afternoon and the following morning he was irrational. The ventricles were tapped several times during the following day, and air escaped on each occasion. He became more quiet and more rational after the release of air from the ventricles. On the second day following ventriculography the condition was more satisfactory, and from this time on it improved progressively. However, the temperature remained elevated and the pulse rate rapid for several days. On September 8 the condition was reported as being the same as before the operative procedure was carried out. The roentgenologist submitted the following report of the ventriculographic studies: "This study reveals dilatation of the left cranial wall, associated with thinning of the bones of the cranial vault, which is more pronounced on the left than on the right. There is associated extreme dilatation of the ventricles, which has resulted in an unbelievable degree of cortical atrophy; practically no cortex is visible on the left and very little on the right. We have never seen such extreme dilatation of the

ventricles. The dilated ventricle on the left practically fills the entire cranial vault except the interpeduncular space and the area below the tentorium. The pituitary fossa is enlarged, and there is complete erosion of the posterior clinoids." It should be noted here that the history of meningitis at an early age was not available at the time the patient was being studied in the Graduate Hospital. The patient was discharged on September 10, unimproved.

When admitted to the Philadelphia Institution for the Feeble Minded one month later, his condition was much the same as previously noted. There has been little change in the physical or mental status since that time. The circumference of the head is 23½ inches (59.67 cm.). There is prominence of the left parietal region. There is horizontal nystagmus with a rotatory element accompanying it which is brought out by lateral gaze in either direction. The slow component is in the direction in which the patient is looking. There is an ocular imbalance. The pupils are round and somewhat eccentric and react rather sluggishly to light. There is a spastic hemiparesis, and the right arm and leg are underdeveloped. The left arm and leg are slightly spastic. The right biceps and triceps reflexes are exaggerated, and there is an arm clonus. A Hoffmann sign is not demonstrable. The left biceps and triceps reflexes are hyperactive. There are patellar and ankle clonus together with a Babinski sign bilaterally. All the deep reflexes of the lower extremities are exaggerated, more so on the right. The abdominal reflexes are hyperactive. The patient is unable to walk but can sit in a wheel-chair unaided. He is able to talk and comprehends most of the things that are said to him. He is generally pleasant and has a rather alert expression. Although the intelligence quotient is 43, he is markedly handicapped by the physical and neurologic defects.

We consider case 3 one of obstructive internal hydrocephalus resulting from basilar meningitis occurring at a very early age. The case illustrates the great adaptability of the brain to abnormal conditions within the skull. In spite of marked ventricular dilatation, with encroachment on the cerebral white matter and thinning of the cortex, the patient has retained a fair amount of intellectual capacity. In view of this, it seems inconceivable that a gross meningeal hemorrhage over the cortex occurring at birth should alone produce marked degrees of congenital spastic palsy and at times complete mental retardation.

CASE 4.—*A low grade idiot with left hemiparesis.*

E. R., a colored girl, aged 12, with an intelligence quotient of 12, was admitted on June 4, 1930. A grandfather was psychotic; otherwise, so far as is known, the family history reveals no neuropathic taint. Both parents are living and well. Five siblings are living and apparently normal. The patient is the oldest child and was born two years before the parents were married. The mother's condition was good during pregnancy, and birth was normal. Dentition began at the usual time; the child walked at 10 months and talked soon after this. The parents said that she seemed to be normal until she was 1 year of age, when "she ate corn before it ripened." Following this dietary indiscretion she had a convulsive seizure. Since then she has had frequent grand mal attacks. At the age of 2, the left arm and leg became paralyzed during a convulsive seizure.

The patient is underdeveloped but well nourished. The head is large in proportion to the size of the body. The pupils are round and equal and react promptly to light and in accommodation. Extra-ocular movements are normal.

The heart and lungs are normal. The deep reflexes are present and active throughout, but exaggerated on the left. The left arm and leg are slightly spastic, and there is a Babinski sign on the left. The patient is able to walk, but in doing so drags the left leg. She has from six to twelve convulsive seizures monthly.

One hundred and two patients manifest cerebral diplegia. These comprise a high percentage of the patients with neurologic manifestations and a rather large percentage of the total number of children examined.

The high percentage of idiots in this group tends to confirm Sachs' and Hausman's [3] statement that the high percentage of idiocy in congenital paralysis indicates more than involvement of the pyramidal tracts. The percentage of our patients showing spastic diplegia appears to be high as compared with the figures usually quoted. Mendelsohn [4] found that 15 per cent of mentally defective persons have infantile spastic paralysis.

TABLE 10.—*Psychologic Classification of Patients with Congenital Spastic Diplegia*

	Number	Percentage of Group	Percentage of Patients with Positive Neurologic Findings	Percentage of All Patients
Morons	6	5.9	3.5	1.7
Imbeciles	23	22.5	13.4	6.6
Idiots	73	71.6	42.7	20.8
Total	102	100.0	59.6	29.1

Table 11 gives a composite summary of certain available information concerning the patients with congenital spastic diplegia; we have indicated roughly the degree of spasticity observed in each case, having divided the group into three divisions: (1) patients with slight spasticity, (2) those with moderate spasticity and (3) those with marked spasticity.

As has already been mentioned, we found considerable relationship between the degree of spasticity and the intellectual level, although there seems to be a wide range in the intelligence quotients of the individual patients in each of the three divisions. The fact that the average intelligence quotient has dropped considerably as the degree of motor defect increased is highly significant. This cannot be ascribed to any great extent to the influence of the motor defect in testing these patients, since the psychologist made due allowance for this in every instance and, when indicated, used a number of different types of tests. For the most part, the best results were obtained by the use of the Kuhlmann and

3. Sachs, B., and Hausman, L.: Nervous and Mental Disorders from Birth Through Adolescence, New York, Paul B. Hoeber, Inc., 1926, p. 234.

4. Mendelsohn, J. J.: A Summary of Nervous and Mental Findings in Feeble-Minded Children, Illinois M. J. **26**:409, 1914.

TABLE 11.—*Patients with Congenital Spastic Diplegia—Composite Summary*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Degree of Spasticity	Physical Defects and Other Conditions
1	W. A.	M	13	2	28	54	Normal	Moderate	Convulsive seizures
2	R. B.	M	18	1	30	4	No history	Moderate	Convulsive seizures
3	J. C.	M	18	1	21	16	No history	Slight	
4	N. C.	M	12	2	35	15	Difficult	Marked	
5	J. E.	M	8	2	18	10	Normal	Moderate	Convulsive seizures
6	L. E.	M	10	1	25	3	Normal	Marked	Convulsive seizures
7	J. F.	M	10	1	37	11	Normal	Moderate	Athetosis
8	A. F.	M	10	3	35	18	Normal	Moderate	
9	O. F.	M	10	1	23	57	Normal	Moderate	
10	A. F.	M	13	1	27	24	Normal	Moderate	Convulsive seizures
11	R. G.	M	19	5	27	25	Normal	Marked	Convulsive seizures
12	P. G.	M	15	1	21	5	No history	Moderate	Convulsive seizures; subtemporal decompression bilaterally
13	J. G.	M	11	1	24	11	Difficult	Moderate	Anterior staphyloma; convulsive seizures
14	J. G.	M	13	2	30	21	Normal	Moderate	
15	W. G.	M	16	5	28	29	Labor difficult	Slight	
16	J. G.	M	8	1	23	10	No history	Moderate	
17	E. G.	M	4	1	16	33	No history	Slight	Convulsive seizures
18	J. H.	M	15	4	31	17	No history	Slight	
19	E. H.	M	13	2	18	1	Normal	Marked	Convulsive seizures
20	J. H.	M	13	2	25	7	Labor induced; forceps delivery	Marked	Convulsive seizures
21	J. H.	M	15	2	29	16	No history	Moderate	Corneal opacity
22	W. J.	M	14	4	29	41	No history	Marked	
23	L. K.	M	7	1	25	32	Difficult	Marked	
24	M. K.	M	19	1	28	46	No history	Slight	
25	W. K.	M	8	1	23	11	No history	Moderate	Oxycephaly; blind; choreo-athetosis
26	D. K.	M	9	2	37	16	No history	Marked	Microcephaly
27	G. K.	M	10	4	27	10	Normal	Moderate	
28	T. L.	M	14	5	29	23	Premature	Slight	
29	J. L.	M	15	5	25	13	Premature	Marked	Athetosis; convulsive seizures
30	O. L.	M	5	2	?	22	No history	Moderate	Athetosis
31	J. L.	M	14	1	23	16	No history	Moderate	
32	J. M.	M	5	2	22	8	Difficult	Moderate	Oxycephaly; blind
33	J. M.	M	11	7	36	1	No history	Marked	Microcephaly; convulsive seizures
34	R. M.	M	16	2	21	10	No history	Marked	Convulsive seizures
35	C. M.	M	13	2	23	70	Normal	Slight	Convulsive seizures
36	H. M.	M	15	?	?	1	No history	Marked	Oxycephaly; convulsive seizures
37	T. M.	M	19	1	40	22	No history	Moderate	
38	D. McD.	M	14	1	23	6	No history	Marked	Convulsive seizures
39	J. McN.	M	11	1	?	18	Normal	Marked	
40	W. McG.	M	10	1	32	7	No history	Marked	Cranial asymmetry; athetosis; convulsive seizures
41	I. L.	M	14	10	35	22	Difficult	Marked	
42	T. N.	M	11	?	?	19	No history	Marked	Athetosis
43	T. O.	M	7	2	?	67	No history	Slight	Blind; hyperactive
44	J. P.	M	16	5	33	3	No history	Marked	
45	G. P.	M	14	7	28	28	Normal	Marked	Convulsive seizures
46	M. P.	M	9	5	29	43	No history	Slight	
47	J. P.	M	14	2	21	36	No history	Moderate	
48	S. R.	M	4	1	23	39	Difficult	Slight	
49	I. R.	M	16	3	28	7	No history	Marked	Convulsive seizures
50	W. S.	M	12	3	28	31	No history	Slight	Convulsive seizures
51	B. S.	M	17	2	24	3	No history	Marked	Convulsive seizures
52	A. S.	M	17	6	36	26	No history	Marked	
53	I. T.	M	18	3	38	5	No history	Marked	Mongolism
54	J. U.	M	12	3	33	32	Difficult	Moderate	
55	B. B.	F	8	4	26	14	No history	Slight	Microcephaly; deaf-mute
56	T. B.	F	6	1	37	26	Difficult	Moderate	
57	M. B.	F	18	1	27	17	Instrumental delivery	Marked	Positive Wassermann reaction
58	M. B.	F	13	2	19	18	Normal	Moderate	Convulsive seizures
59	J. B.	F	7	1	36	26	No history	Slight	
60	J. B.	F	9	1	26	17	Premature	Marked	Congenital cataracts; convulsive seizures
61	E. B.	F	8	2	23	13	No history	Marked	
62	M. C.	F	11	4	21	10	Normal	Marked	
63	M. C.	F	11	2	22	33	No history	Slight	
64	E. C.	F	20	5	30	37	No history	Moderate	Spasticity plus cerebellar ataxia
65	D. C.	F	18	2	19	10	Normal	Marked	

TABLE 11.—*Patients with Congenital Spastic Diplegia—Composite Summary—Continued*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Degree of Spasticity	Physical Defects and Other Conditions
66	E. D.	F	17	1	20	13	No history	Marked	Positive Wassermann reaction
67	C. D.	F	15	1	20	3	No history	Marked	Convulsive seizures
68	H. D.	F	15	2	33	6	Normal	Moderate	
69	T. E.	F	17	1	19	15	No history	Marked	
70	M. F.	F	11	2	28	30	Normal	Moderate	
71	M. F.	F	13	3	35	7	No history	Moderate	
72	H. G.	F	16	2	22	10	Normal	Moderate	Macrocephaly
73	I. G.	F	16	1	30	7	Normal	Moderate	
74	G. G.	F	7	6	22	15	Normal	Moderate	
75	G. G.	F	13	3	28	33	Normal	Slight	
76	S. H.	F	13	6	32	5	Normal	Marked	
77	G. H.	F	18	2	29	25	Normal	Moderate	
78	A. H.	F	16	1	19	3	No history	Marked	Convulsive seizures
79	D. H.	F	11	1	18	12	Normal	Moderate	Convulsive seizures
80	E. K.	F	9	6	32	29	No history	Moderate	Microcephaly; convulsive seizures
81	S. K.	F	5	4	20	13	Difficult	Marked	Oxycephaly; blind
82	E. K.	F	15	5	28	5	Normal	Moderate	Convulsive seizures
83	M. K.	F	10	2	26	22	Normal	Marked	
84	S. L.	F	9	1	19	17	Difficult	Marked	
85	A. L.	F	13	3	48	21	Normal	Moderate	
86	I. L.	F	15	1	45	7	Normal	Moderate	Athetosis
87	G. McN.	F	17	2	?	11	No history	Marked	
88	V. O'D.	F	11	3	29	32	Normal	Slight	
89	H. O.	F	5	6	30	17	No history	Marked	
90	S. O.	F	11	4	31	60	No history	Slight	
91	A. O.	F	6	4	32	10	Difficult	Marked	
92	M. P.	F	8	1	24	30	Premature	Moderate	
93	A. P.	F	12	4	31	22	No history	Slight	Choreiform movements
94	M. P.	F	8	3	30	11	Difficult	Marked	
95	D. R.	F	5	6	36	14	No history	Slight	Choreo-athetosis; convulsive seizures
96	M. S.	F	4	1	25	11	No history	Marked	Convulsive seizures
97	R. S.	F	15	4	38	53	Normal	Moderate	
98	C. S.	F	15	4	22	4	No history	Marked	
99	M. S.	F	17	1	29	6	No history	Moderate	Convulsive seizures
100	L. S.	F	15	4	36	6	Normal	Marked	Cranial asymmetry; convulsive seizures
101	S. S.	F	3	3	34	8	No history	Slight	Oxycephaly; blind; convulsive seizures
102	C. S.	F	8	1	?	7	No history	Marked	Microcephaly; choreiform movements; convulsive seizures

TABLE 12.—*Degree of Spasticity as Related to Intellectual Level*

Degree of Spasticity	Number of Patients	Average I. Q.
Slight	20	32.80
Moderate	38	19.50
Marked	44	12.30
Total	102	19.03

Stanford revisions of the Binet-Simon scale. (This is in keeping with Doll, Phelps and Melcher's [5] findings in their work in a group of patients showing motor defects of a spastic or rigid type.) Considerable difficulty was experienced in estimating accurately the exact degree of spasticity present in a number of the helpless children with very low grade intelligence because of the marked disuse atrophy present.

5. Doll, E. A.; Phelps, W. M., and Melcher, R. T.: Mental Deficiency Due to Birth Injuries, New York, The Macmillan Company, 1932.

As observed in table 12, the average intelligence quotient is highest in patients showing the least amount of spasticity and lowest in the group with marked spastic palsy. The following cases serve to illustrate better the type of patient considered as having a spastic diplegia probably unrelated to injury at birth.

CASE 5.—*A helpless low grade idiot with a poor family background who presents cranial asymmetry, an advanced degree of spastic paralysis involving all four extremities and convulsive seizures.*

L. S., a white girl, aged 15, with an intelligence quotient of 6, was admitted on May 12, 1929. A paternal great-aunt was epileptic and "insane." A paternal first cousin died of epilepsy, and another has convulsive seizures. A paternal first cousin was feebleminded and died in a state institution at Vineland, N. J. Five brothers and 3 sisters died of epileptic convulsions; an older sister, who is living and well, has 2 children who have convulsive seizures; 3 other siblings are living and well. The father died at the age of 51 of carcinoma of the stomach. The mother is illiterate and obviously mentally defective. She is said to make a practice of defrauding insurance companies in various ways. Her activities are now being investigated by several companies. The mother's health was good during gestation; labor was short and easy, and birth was considered normal. Four days after birth the patient had a convulsive seizure. Following this attack seizures occurred at frequent intervals and increased in severity for a number of years, but no seizures have occurred since 1927. The patient lies helplessly on her back in bed, with the thighs in a position of outward rotation, the lower legs flexed at the knees and the soles of the feet approximated, which gives her a froglike appearance. The head is broad but narrow in its anteroposterior diameter. The pupils are round and equal and react promptly to light and in accommodation. There is ocular imbalance, with divergent squint and horizontal nystagmus. Vision appears to be good. The arms are moderately spastic and held in a position of flexion. The legs are markedly spastic. The biceps and triceps reflexes are hyperactive, and the patellar and achilles jerks are markedly exaggerated. Plantar irritation produces an extensor response of the right great toe, and there is ankle clonus on the right. Pain sense is apparently normal.

CASE 6.—*An underdeveloped but well nourished low grade imbecile with a small head, cranial asymmetry, spastic diplegia, contraction deformities and convulsive seizures.*

G. P., a white boy, aged 14, with an intelligence quotient of 28, was admitted on June 7, 1929. The parents are living and well; a sister is psychotic. Birth was normal. The child's condition during the first year of life is not known. At the age of 1½ years he began to have convulsive seizures, which have occurred at frequent intervals since. The patient is underdeveloped for his age but well nourished. The head is small in proportion to the size of the body and asymmetrical. There is a convergent squint, but the pupillary reactions are normal. The heart and lungs are normal. Both the upper and the lower extremities are extremely spastic, and there are contraction deformities of both feet. The biceps, triceps and patellar reflexes are hyperactive. The achilles tendon reflexes cannot be elicited because of the deformity of the feet. A Babinski sign cannot be elicited. The superficial reflexes are normal. The patient is able to sit in a wheelchair unaided but cannot talk or walk. Speech is limited to a few unintelligible sounds. There is no evidence of glandular dysfunction. He is uneducable and untrainable. He has numerous grand mal attacks, averaging fifteen monthly.

CASE 7.—*An underdeveloped, poorly nourished low grade moron with spastic diplegia.*

R. S., a white girl, aged 15, with an intelligence quotient of 55, was admitted on May 6, 1925. The family history reveals no neuropathic taint. The parents are living and well. Three siblings are living and normal. Birth was entirely normal. The child was small and did not appear to be normal at birth. She was breast fed for one year; growth and development were retarded. Dentition did not begin until 2 years of age. She has never learned to walk and did not begin to talk until the age of 5.

The patient sits unaided, feeds herself, has fair language ability and comprehends practically everything that is said to her. She is underdeveloped and poorly nourished. The head is well formed and in proportion to the size of the body. The pupillary responses and extra-ocular movements are normal. The heart, lungs and abdomen are normal. There are no gross deformities of the upper extremities. The patient has good use of her arms and hands. The biceps and triceps reflexes are normal. The lower extremities are markedly spastic, with poorly developed musculature. There is talipes equinovarus bilaterally. The patellar and achilles tendon reflexes are difficult to elicit because of the spasticity. Ankle clonus cannot be produced, but there is a Babinski sign bilaterally.

CASE 8.—*A poorly developed, low grade imbecile with spastic palsy of both lower extremities and one arm.*

T. B., a white girl, aged 5 years, with an intelligence quotient of 26, was admitted on Oct. 7, 1931. The family history reveals no neuropathic taint. The parents are living and well. Two siblings younger than the patient are thought to be normal. The mother's pregnancy was uneventful; labor was prolonged; birth was difficult, but instruments were not used. Development was retarded. The child has not learned to talk or walk. She speaks only a few simple words. She is underdeveloped but fairly well nourished. She is rather pleasant and smiles when stimulated. She lies helplessly in bed and is unable to sit unaided. There is cranial asymmetry; the head is narrow in the anteroposterior diameter. The pupils react promptly to light and in accommodation, and the extra-ocular movements are normal. The right pupil is slightly larger than the left. The heart, lungs and abdomen are normal. The lower extremities are poorly developed, and the musculature is flabby. Both legs are spastic, and there is slight spasticity of the right arm, although the patient has some voluntary control of the involved extremities. The right biceps and triceps reflexes are extremely exaggerated. The left triceps and biceps jerks cannot be elicited. The patellar and achilles tendon reflexes are exaggerated. There is a Babinski sign bilaterally.

CASE 9.—*An underdeveloped, poorly nourished idiot with a marked spastic diplegia and convulsive seizures.*

J. B., a white girl, aged 9 years, with an intelligence quotient of 17, was admitted on Oct. 27, 1928. The family history reveals no neuropathic taint. The parents are living and well. One sibling, younger than the patient, is normal. The patient was born five weeks before term. Labor was brief and is said to have lasted only thirty minutes. The child weighed 4¾ pounds (2,154.56 Gm.) at birth and cried immediately, but appeared to be weak and was unable to nurse at the breast for the first two months. Development was retarded, and the child did not hold up her head until 8 months of age. She could sit unsupported at 1 year, talked at 2½ years and walked when 3½ years old. She had been totally blind since birth. Convulsive seizures began at the age of 6 years and have occurred at frequent intervals since.

The patient is underdeveloped and poorly nourished. The head is large in proportion to the size of the body. There is microphthalmia, with bilateral congenital cataracts. The heart, lungs and abdomen are normal. The extremities are poorly developed, with atrophic musculature. The arms are mildly spastic; the lower extremities are markedly spastic. The biceps and triceps reflexes are present and hyperactive. The patellar and achilles tendon reflexes are extremely exaggerated. There is a Babinski sign bilaterally. The superficial reflexes are normal. The patient has an average of twenty convulsive seizures each month.

CASE 10.—*A low grade helpless idiot with spastic diplegia. Attitude of universal flexion; clubfeet.*

D. C., a white girl, aged 18, with an intelligence quotient of 10, was admitted on March 13, 1925. The family history is negative for neuropathic tainting. The mother's condition was good during pregnancy; labor and birth were considered normal. Dentition was normal; the child is said to have learned to walk at the age of 1 year, but at about that age the parents noticed that she did not appear as intelligent as other children. At 2 years she had the first convulsive seizure, which was severe and is said to have lasted for one-half hour. When 2 years of age she had an even more severe convulsion. She never learned to talk but could hum tunes. At the age of 5 she became restless and destructive. With advancing age she became more and more a burden to the family until placement became necessary.

The patient is poorly developed and undernourished and assumes an attitude of universal flexion. She can sit unaided but cannot walk or talk and has to be fed with a spoon. At times she induces vomiting by thrusting her fingers down her throat. She has stereotyped mannerisms. The head is small in proportion to the size of the body but is symmetrical. There is slight internal strabismus. The thorax is poorly developed, with a Harrison groove. The heart and lungs are normal. The abdominal wall is relaxed, with prominent veins. The upper extremities are slightly spastic. The lower extremities are markedly spastic, and there is equinovarus of the right foot. The biceps and triceps reflexes are present and active. The patellar and achilles tendon reflexes cannot be elicited, owing to spasticity. There is a Babinski sign on the right. Plantar irritation on the left produces little response. The superficial reflexes are normal. Pain sense is present; other types of sensation cannot be tested.

CASE 11.—*A low grade idiot with spastic diplegia and epilepsy.*

A. O., a white girl, aged 6, with an intelligence quotient of 10, was admitted on Feb. 14, 1931. The maternal grandfather has been a patient in the Philadelphia Hospital for Mental Diseases for the past twenty years. The family history otherwise revealed no neuropathic taint. The mother and father are living and well. The mother's condition was good during pregnancy, but labor was prolonged and difficult, and instruments were used. The child weighed 7½ pounds (3,401.93 Gm.) at birth and appeared to be normal. She was bottle fed. She cut teeth at the usual age, but did not learn to walk or talk. At the age of 3 months, she had her first convulsive seizure, and attacks occurred at frequent intervals for several years. She had at one time as many as twenty convulsions within twenty-four hours, but for the past two years no attacks have been observed. During the first year of life she had scarlet fever and was treated for rickets.

The patient is poorly developed and poorly nourished. She can sit unaided, but cannot walk, feed herself or talk. The head is of normal size and contour. The eyes are normal, except for slight internal strabismus; the pupillary reaction to light and in accommodation is prompt. The muscles of the face and neck are

fairly well developed and are not spastic. There is a moderate degree of spasticity of all four extremities, which is somewhat more marked in the legs. The musculature of the extremities is poorly developed, and the legs are held in a position of acute flexion, with the thighs on the abdomen and the lower part of the legs on the thighs, but can be passively extended. The deep tendon reflexes are exaggerated, but a Babinski sign cannot be elicited. Sensation cannot be adequately tested, but pain sense does not appear to be impaired, as elicited by pinpricks.

Since cerebral diplegia was first described in 1862 by Little,[6] the cause of this condition has been the subject of much scientific interest, and various writers have expounded a number of theories. In 1875, Erb and Charcot [7] described primary lateral sclerosis in adults, and cases were soon discovered in children, which were really examples of infantile diplegia. McNutt,[8] in 1885, gave meningeal hemorrhage as the cause of infantile spastic states dating from the time of birth and associated with difficult labor, a view which gained widespread credence and is still advocated by many as a highly important cause of this condition. Collier, in an article published in the *Lancet* in November 1923, and in another in *Brain,*[9] showed rather conclusively that in only a small proportion of these cases is there any evidence of hemorrhage.

Purves-Stewart [10] stated in the most recent edition of his textbook that "in the great majority of cases the disease is due to primary upper neuronic degeneration of unknown cause occurring during intra uterine life." He also stated that the spasticity may tend to improve somewhat as the child grows up. This we believe is possible to a slight degree if the child is given constant physical training, orthopedic care, massage and other treatment, which is possible only for the patients with mildly spastic paralysis seen in institutions who have sufficient intelligence for cooperation. It has been observed, in consonance with this point of view, that if allowed to lie unmolested in bed with a minimum of manipulation patients tend to become progressively more spastic. In fact, a number of patients who were not considered spastic at the time of admission are now definitely so. A possible explanation for this may be found in the

6. Little, W. J.: On the Influence of Abnormal Parturition, Difficult Labor, Premature Birth, and Asphyxia Neonatorum on the Mental and Physical Condition of the Child Especially in Relation to Deformities, Tr. Obst. Soc. London **3**:293, 1861.

7. Erb and Charcot, quoted by Collier.[9]

8. McNutt, S. J.: Double Infantile Spastic Hemiplegia, with Report of a Case, Am. J. M. Sc. **89**:57 (Jan.) 1885; Apoplexia Neonatorum, Am. J. Obst. **18**:73 (Jan.) 1885.

9. Collier, J.: The Pathogenesis of Cerebral Diplegia, Brain **47**:1 (Feb.) 1924.

10. Purves-Stewart, J.: The Diagnosis of Nervous Diseases, London, Edward Arnold & Co., 1931, p. 419.

report of three cases by Alpers,[11] in which there was diffuse progressive cortical degeneration, with loss of ganglion cells in the third cell layer. Asphyxia was considered an etiologic agent in one case, and a toxic process was thought to be operative in the others. There are, of course, other reasons for the advancement of the clinical manifestations, such as cerebral vascular accidents and anoxemia occurring during convulsive seizures.

Strümpell,[12] in 1885, described cases of postnatal diplegia and infantile hemiplegia due to polio-encephalitis and gave this as the initial pathologic condition for infantile spastic states in general. Collier [9] stated that more recent evidence has confirmed the truth of this (Strümpell's [12]) assertion that polio-encephalitis is a common cause of postinfantile hemiplegia and that acquired diplegia with some initial symptoms may be of this nature. Brissaud,[13] in 1894, considered prematurity of birth an essential cause of Little's disease on the basis of myelogeny and quoted Flechsig as stating that what takes three weeks to grow in the pyramidal tract in intra-uterine life will take three years or will never grow in the extra-uterine life of prematurely born patients, and thence arises the spastic paralysis.

Freud,[14] in 1897, postulated that in all instances diplegia dating from birth really has its pathologic origin long before birth; that the hypothesis of meningeal hemorrhage has no basis; that 40 per cent of all cases of diplegia dating from birth are without possible factors connected with birth, not being due to premature, precipitate, prolonged or instrumental birth, or to asphyxia or postnatal convulsions, and that the only cerebral paralysis which results from difficult labor occurs when the brain is lacerated, which results in monoplegia or hemiplegia, rarely diplegia.

In 1908, McCarrison [15] described what he called "nervous cretins" —idiots with general spastic paralysis of the body and limbs, strabismus and nystagmus, who showed diplegia toward the end of the first year of life. He considered diplegia due to toxic processes resulting from deficiency in thyroid and parathyroid functions.

Ford, Crothers and Putnam [16] attributed only a small percentage of cases of cerebral palsy to injury at birth and concurred with Freud and Collier in the belief that congenital cerebral diplegia is apparently unrelated to injury at birth or meningeal hemorrhage.

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11. Alpers, B. J.: Diffuse Progressive Degeneration of the Gray Matter of the Cerebrum, Arch. Neurol. & Psychiat. **25**:469 (March) 1931.

12. Strümpell, quoted by Collier.[9]

13. Brissaud, quoted by Collier.[9]

14. Freud, S.: Die infantile Cerebrallähmung, Vienna, Alfred Hölder, 1897.

15. McCarrison, R.: Observations on Endemic Cretinism, Proc. Roy. Soc. Med. (M. Sect.) **2**:1, 1908.

16. Ford, F. R.; Crothers, B., and Putnam, M. C.: Birth Injuries of the Central Nervous System, Baltimore, Williams & Wilkins Company, 1927.

In our group of patients there are a small number who present a rather characteristic picture which sets them apart from the majority of children exhibiting congenital spastic palsy. These few patients have a more alert and natural facial expression and seem more cognizant and interested in their surroundings, but at the same time are unable to express themselves because of a speech defect. They also frequently

TABLE 13.—*Patients with Neurologic Conditions Possibly Resulting from Trauma at Birth*

Case and Name	Sex, and Age in Years	Order of Birth	Age of Mother	I.Q.	Character of Birth	Neurologic Condition	Comment
1 L. D.	M 15	7	31	54	No history	Speech defect; double athetosis; spastic diplegia with element of rigidity; Babinski sign bilaterally	Patient has an alert facial expression and excellent comprehension but has great difficulty in making himself understood
2 J. D.	M 15	4	37	58	Difficult; instrumental delivery	Slight speech defect; spastic triplegia; athetoid movements of right arm; Babinski sign bilaterally	Although usually good-natured, patient has uncontrollable temper tantrums
3 M. H.	M 8	1	17	33	No history	Marked speech defect; marked spastic diplegia; athetoid movements; Babinski sign bilaterally	Alert, pleasant facial expression; always good-natured; good comprehension
4 J. L.	M 9	1	44	29	No history	Marked speech defect and spastic diplegia; no Babinski sign	Good comprehension; alert facial expression; always good-natured
5 J. M.	M 10	6	27	59	Difficult, breech presentation; delayed animation	Explosive type of speech; double athetosis; dyskinesia; Babinski sign bilaterally	Alert expression; excellent comprehension; always good-natured
6 C. M.	M 16	1	26	45	Difficult; instrumental delivery	Explosive type of speech; double athetosis; marked spastic diplegia with an element of rigidity; Babinski sign bilaterally	Good comprehension; has great difficulty making himself understood; has frequent attacks of agitated depression when he is self-abusive and has suicidal tendencies
7 A. L.	F 12	2	36	53	Premature, difficult	Marked speech defect; spastic diplegia; choreo-athetosis	Alert; good comprehension; eager to learn
8 M. Z.	F 14	2	38	35	Long labor; birth considered normal	Speech defect; poor muscular coordination; spastic diplegia; Babsinski sign bilaterally	Fairly alert and generally pleasant; has shown drop in mental level in spite of intensive training

exhibit a diplegia of a somewhat rigid rather than of a purely spastic type, although in most instances a Babinski sign can be elicited. Dyskinesias and abnormal movements of an athetoid type are usually a part of the clinical picture.

Although for 3 of these patients a history of the birth is lacking, it is significant that for none of the remaining is there a history of normal birth. Furthermore, in spite of marked physical handicaps and a motor disorder of speech, the patients in this group possess a degree of

intelligence greater than might be expected. Also, the muscles of the neck and face are involved to a greater degree than is commonly seen in patients presenting the usual picture of congenital spastic diplegia. The condition presented by these patients may be true palsy due to injury at birth, but, on the other hand, it may represent an irregular distribution in myelin formation, which will be discussed in greater detail elsewhere in the article.

The following cases serve better to illustrate the problems presented by this type of patient.

CASE 12.—*A well nourished, well developed patient with a marked speech defect, abnormal movements and spastic diplegia, with intelligence of a low grade moron.*

J. McI., a white boy, aged 10, with an intelligence quotient of 59, was admitted on June 8, 1926. The family history reveals no neuropathic taint. The mother was not well during gestation; labor began at term, but was prolonged. The child was born by breech presentation, and delivery is said to have been prevented for one-half hour by the nurse to permit the arrival of the physician. Vigorous means were necessary to resuscitate the child after delivery, an hour and one-half being required to accomplish this. A convulsive seizure occurred as soon as respiration was induced; it lasted a number of hours. Nourishment was refused for the first six days after birth, but from then on the child was breast fed until he was 19 months of age. Spasticity of the extremities is said to have been noted immediately after birth. The child was under the care of competent physicians and received massage and orthopedic treatments prior to admission.

The patient is somewhat undernourished and underdeveloped. The head is of normal size and contour. The eyes are normal. Speech is indistinct, and the boy exhibits constant athetoid movements of the face, trunk and extremities. These movements are aggravated by attempts to perform voluntary motor movements. The head is pulled toward the left shoulder by spasmodic movements, and at the same time the mouth is distorted. There is a slight flexion contracture of the left wrist, and the tendons of the heel are shortened. The boy walks with difficulty on his toes, with the knees in apposition. All the extremities are spastic. The deep reflexes are exaggerated about equally. There is a Babinski sign bilaterally. The boy has poor muscular coordination and control. The exteroceptive senses are normal, but the kinesthetic sense is impaired. The patient has been a favorite since admission and has received more than his share of attention from the nurses, teachers, physical therapeutists and physicians. When admitted, he was unable to walk, and although he attempted to enunciate words he could not be understood. He appeared to comprehend what was said to him and attempted to obey commands to the best of his ability. He has always been pleasant, and obedient. When tested at the age of 2½ years by the Kuhlmann revision of the Binet-Simon tests, he was found to have an intelligence quotient of 77 and was considered as belonging in the group of patients with borderline deficiency. Since then he has received extensive physical therapy and academic training, but the intellectual advancement has been slower than was anticipated, in spite of the marked improvement in physical accomplishments. When he was tested in 1930 by the Stanford revision of the Binet-Simon scale, the mental age was 4 years (intelligence quotient, 63), and according to the same type of test the mental age is now 5 years and 6 months (intelligence quotient, 59), full allowance being made each time for motor and speech defects. Thus, within

three years the mental age has increased only 1½ years. We consider the patient to be definitely mentally deficient, as he failed to pass a number of tests which are in no way related to motor handicaps. He showed no more scattering in the tests than would be expected in a patient with a familial type of mental deficiency without neurologic involvement. In the light of our present knowledge, this condition must be considered as probably resulting from trauma at birth, but that a subarachnoid hemorrhage overlying the cortex could have produced the clinical picture observed seems improbable. Multiple areas of cellular destruction secondary to the prolonged asphyxia or subependymal hemorrhages involving primary germinal foci are more likely etiologic factors. The condition differs from the usual congenital spastic diplegia in that the face is involved, speech is severely affected and abnormal involuntary movements are present.

CASE 13.—*A well developed, well nourished boy with spastic diplegia, muscular incoordination and athetosis who has spells of agitated depression with suicidal tendencies.*

C. M., a white boy, aged 16, with an intelligence quotient of 45, was admitted on July 9, 1930. The family history reveals no neuropathic taint. The parents are living and well. There are no siblings. The mother's condition was good during pregnancy; labor was difficult, and the child was born by instrumental delivery. He was considered to be normal at birth. Dentition was normal. He could not sit unaided at the end of the first year and did not learn to walk until he was 8 years of age. He had whooping cough, chickenpox and measles between the ages of 3 and 5 years. When 7, he began to have periods of excitement and restlessness during which he became much depressed and attempted to injure himself. Commitment to an institution then became necessary.

The patient is well developed and well nourished. He has a marked speech defect, and although his vocabulary is fair it is extremely difficult to understand what he is attempting to say. The head is of normal size and contour. The pupils are round and equal and react promptly to light and in accommodation. Extraocular movements are normal. The extremities are well developed, but there is rather marked spasticity, with frequent athetoid movements. The gait is spastic, and he walks on his toes with the legs partially flexed at the knees. All the deep reflexes are exaggerated, and there is a Babinski sign bilaterally. The sensory system is normal.

Since admission to the institution there has been some improvement in the patient's behavior, and he has shown a slight response to training. He has rather frequent attacks during which he becomes hyperactive and at the same time depressed. During these periods it is necessary to institute mechanical restraint to prevent him from injuring himself, and on a number of occasions he has attempted to commit suicide by strangulation. He realizes when he is about to become upset and frequently asks to be placed in restraint. The condition is aggravated by visits from relatives. Recently these periods have become less frequent.

In spite of the strong presumptive evidence that the physical and mental impairment in these cases has resulted from injuries sustained at birth, there is still cause for reasonable doubt as to whether the trauma at birth is the sole etiologic factor. We believe that considerably more than a history of trauma at birth is necessary to substantiate such a diagnosis.

Doll, Phelps and Melcher, in their recently published book [5] based entirely on an exhaustive study, chiefly psychologic, of 12 patients, 5 of whom had "extra-pyramidal lesions, characterized by athetosis," expressed the belief that trauma at birth, with cerebral hemorrhage, was the chief cause of the neurologic manifestations and the intellectual impairment observed. The type of hemorrhage or hemorrhages thought to be responsible for the wide variety of neurologic signs noted in their cases is not clearly defined, and in view of the findings in our series it is believed that they overevaluated the possible factor of trauma at birth as an etiologic agent.

That great care must be exercised in making a definite diagnosis of a neurologic condition thought to result from an injury at birth is well illustrated by one of our cases, which bears some resemblance to the first case cited by Doll, Phelps and Melcher.[5] An underdeveloped girl, aged 5 years, is the elder of like-sexed but probably dizygotic twins born by means of cesarean section. She is a low grade idiot, while the sister is a normally developed, apparently healthy child whose intelligence quotient is 79. There are 2 other siblings younger than the patient, who also were born by cesarean section, who are considered by the parents to be normal. The patient's head is slightly smaller than normal, asymmetrical and flattened over the occiput, and the sagittal suture in that area is depressed. The biparietal diameter is broad in proportion to the anteroposterior diameter. She appears to be blind, except for perception of light, and there is an ocular imbalance. The left arm is slightly spastic and is moved less freely than the right. The left leg is slightly hypertonic but is less involved than the ipsilateral arm. The right arm and leg are hypotonic. The deep reflexes are difficult to elicit, but are more readily produced on the left. Plantar irritation on the left at times produces an extensor type of response in the great toe.

The mother said that she did not observe any abnormality in the child until she was 5 weeks old, when she noted a peculiar stare in her eyes. A week later the child had a series of convulsive seizures. The maternal grandmother said that she realized that the child was not normal from the time of birth but did not communicate her suspicions to the mother. The patient has always been irritable and difficult to feed. She was still taking a bottle when admitted in January 1933. She lies helplessly in bed and cannot sit unaided. She cannot speak, but cries whenever disturbed.

Cesarean section was indicated in this case because of a contracted pelvis in the mother. Had the mother been permitted to go into labor, which undoubtedly would have been difficult and prolonged, and had this child been eventually delivered with the aid of forceps, which might have produced some observable injuries to the child's head, it is certain that this patient's condition, in view of the history and physical findings,

would have been considered as having resulted from trauma at birth. In view of reports of such cases it must be concluded that in most instances more than a history of difficult labor is necessary before a diagnosis of injury due to birth can safely be made, regardless of the physical findings.

TABLE 14.—*Psychologic Classification of Patients with Spastic Hemiplegia or Monoplegia*

	Number	Percentage of Group	Percentage of Patients with Positive Neurologic Findings	Percentage of All Patients
Morons	5	35.7	2.9	1.4
Imbeciles	6	42.9	3.5	1.7
Idiots	3	21.4	1.7	0.9
Total	14	100.0	8.1	4.0

TABLE 15.—*Patients with Spastic Hemiplegia or Monoplegia—Composite Summary*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Parts Involved	Physical Defects and Other Conditions
1	W. A.	M	8	4	28	28	"Blue baby"	Right leg	Macrocephaly
2	R. B.	M	9	7	32	39	Normal	Left leg	All deep reflexes hyperactive
3	D. H.	M	10	4	29	60	Normal	Left arm and leg	
4	E. K.	M	10	1	30	15	Normal	Right arm	Convulsive seizures
5	J. M.	M	15	3	19	53	Difficult	Right leg	Macrocephaly
6	J. McM.	M	9	2	26	34	No history	Right leg	
7	C. R.	M	11	3	21	54	No history	Left face, right arm and leg	Congenital cataracts
8	W. R.	M	12	2	20	55	No history	Left arm and leg	
9	E. S.	M	10	3	33	41	No history	Left arm and right leg	
10	H. H.	F	6	2	22	37	No history	Left arm and leg	Microcephaly; internal strabismus
11	C. H.	F	4	5	49	27	No history	Left leg	Convulsive seizures
12	L. M.	F	15	?	?	7	Normal	Right arm and leg	
13	C. R.	F	5	1	23	8	Born by cesarean section	Left arm and leg	Cranial asymmetry; blind; history of convulsive seizures
14	T. V.	F	13	6	31	52	No history	Right arm and leg	Left internal strabismus; convulsive seizures

Fourteen patients in this series have spastic hemiplegia or monoplegia. As may be observed in table 14, which shows the psychologic classification of this group, most of the patients have a relatively high intelligence quotient as compared with the patients showing spastic diplegia. We expected to obtain a history of difficult or abnormal birth in most of the cases, but, contrary to these expectations, the incidence of possible trauma at birth is very low in cases in which a history was available.

CASE 14.—*A low grade moron with a facial weakness of central type on the left and spastic hemiparesis on the right.*

C. R., a colored boy, aged 11, with an intelligence quotient of 54, was admitted on Nov. 16, 1925. Little is known concerning the patient's ancestors. The father's whereabouts are unknown. The mother is living and well. Two siblings, a boy and a girl, are patients in the institution at present. The brother, aged 12, is a middle grade moron, with spastic hemiparesis on the left. The sister, aged 14, is a high grade imbecile who shows no neurologic defects. She has congenital

TABLE 16.—*Psychologic Classification of Patients Showing Hyperreflexia and a Babinski Sign Without Evidence of Spasticity*

	Number	Percentage of Group	Percentage of Patients with Positive Neurologic Findings	Percentage of All Patients
Morons	2	8.3	1.2	0.6
Imbeciles	12	50.0	7.0	3.4
Idiots	10	41.7	5.8	2.8
Total	24	100.0	14.0	6.8

TABLE 17.—*Patients Showing Hyperreflexia and a Positive Babinski Sign Without Evidence of Spasticity—Composite Summary*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Gestation and Labor	Physical Defects and Other Conditions
1	R. A.	M	14	1	25	56	Normal	
2	E. A.	M	11	6	31	43	Normal	
3	R. C.	M	10	7	42	24	No history	
4	E. D.	M	11	1	17	23	Normal	
5	A. G.	M	11	6	29	30	No history	
6	J. K.	M	10	1	24	15	No history	Convulsive seizures
7	F. K.	M	9	4	35	27	No history	Convulsive seizures
8	S. L.	M	16	1	23	36	No history	Cryptorchidism
9	F. M.	M	13	3	?	21	Normal	Sydenham's chorea; convulsive seizures
10	G. R.	M	10	1	22	45	Normal	Cranial asymmetry; dystonic movements
11	C. V.	M	14	2	30	14	Premature	Facial asymmetry; convulsive seizures
12	T. W.	M	5	6	44	17	Difficult	Convulsive seizures
13	J. Z.	M	17	1	23	12	No history	Deaf-mute
14	A. B.	F	15	1	20	13	No history	Macrocephaly; deaf-mute
15	M. D.	F	14	5	33	36	Normal	
16	A. D.	F	15	1	19	34	Difficult	
17	C. F.	F	13	3	23	5	No history	Convulsive seizures
18	R. H.	F	8	3	30	28	Difficult	Convulsive seizures
19	D. K.	F	12	2	33	31	No history	Convulsive seizures
20	G. M.	F	11	2	21	34	No history	
21	C. O.	F	13	?	?	39	No history	
22	M. R.	F	7	3	32	27	Normal	Mongolism
23	L. W.	F	11	3	?	62	No history	Choreiform movements
24	H. W.	F	13	1	18	10	No history	Convulsive seizures

cataracts and occasional convulsive seizures. The mother has married a second time and has 1 child by this union, who is said to be normal. There is no available history concerning the nature of the patient's birth or early development. At present he is quiet and fairly well behaved. He has a stellate cataract in each lens and ptosis of the left upper eyelid. There is facial weakness of central type on the left and spastic hemiparesis on the right, with a flexion deformity of the right arm and contraction of the tendon of the right heel. The right arm and leg are underdeveloped. The boy attends the occupational therapy, physical training and kindergarten classes. He has shown slow but steady progress in school.

Patients with convulsive seizures tend to have a lower grade of intelligence than patients who are free from epilepsy. It appears that a convulsive disorder in itself may be responsible for the neurologic signs observed. However, it is difficult to account for the neurologic conditions observed in the other patients except on the basis of factors similar to those giving rise to congenital spastic diplegias. Such factors may have been operative to a lesser degree in these patients, producing only a minimum amount of damage to the pyramidal system.

CASE 15.—*A well developed, well nourished imbecile with hyperreflexia and a Babinski sign unilaterally.*

A. D., a white girl, aged 15, with an intelligence quotient of 34, was admitted on April 6, 1925. Little is known concerning the patient's ancestors. The mother

TABLE 18.—*Patients with Hydrocephalus with Involvement of the Pyramidal Tracts—Composite Summary*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Neurologic Status	Etiology
1	T. B.	M	10	4	29	53	Normal	Spastic paraplegia	
2	J. N.	M	14	?	?	29	No history	Ptosis of upper eyelid; spastic diplegia; convulsive seizures	(Positive Wassermann reaction of blood)
3	J. S.	M	15	3	?	42	Normal	Flaccid paraplegia; lumbar spina bifida	
4	W. W.	M	12	3	23	43	Normal	Spastic quadriplegia	Meningitis at 12 months
5	A. F.	F	15	2	23	15	No history	Spastic hemiparesis; convulsive seizures	
6	G. J.	F	3	11	33	40	No history	Hyperreflexia; positive Babinski sign	
7	A. V.	F	15	5	35	22	No history	Spastic diplegia	Meningitis at early age

and father were born in Italy. The mother was in good health during pregnancy; labor was difficult, but birth was spontaneous. The child appeared to be normal at birth. She had a severe illness during the first year, the exact nature of which is not known. She is said to have had typhoid, measles, whooping cough and scarlet fever between the ages of 20 months and 5 years. There is a history of nocturnal epileptiform seizures, but these have not been observed in recent years. When admitted, the intelligence quotient was 34 with the Stanford-Binet scale, but has since dropped to 18. Her maximum ability had apparently been reached at the time of the first psychometric examination. The patient is well developed and well nourished. The head is of normal size and contour; the eyes are normal. The heart and lungs show no pathologic changes. The extremities are well developed, with no deformities. The patellar and achilles tendon reflexes are exaggerated but equal. There is a Babinski sign on the right. The superficial reflexes are normally active. Sensation is normal.

Seven patients exhibit hydrocephalus to a noteworthy degree and involvement of the corticospinal tract. The probable etiology is indi-

cated in only 2 cases. The positive Wassermann reaction in one may have no etiologic significance. The fact that all the patients with hydrocephalus exhibit signs of involvement of the pyramidal tracts is interesting from a neuro-anatomic standpoint.

Thirteen patients exhibit athetosis or movements of a choreo-athetoid type.

TABLE 19.—*Patients with Abnormal Movements—Athetosis or Choreo-Athetosis Present in All Cases—Composite Summary*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Neurologic Status
1	L. D.	M	15	7	31	54	No history	Spastic diplegia with element of rigidity; speech defect
2	J. D.	M	15	4	37	58	Difficult instrumental delivery	Speech defect; spastic triplegia; athetoid movements of right arm
3	J. F.	M	10	1	37	11	Normal	Spastic diplegia
4	M. H.	M	8	1	17	33	No history	Speech defect; spastic diplegia
5	W. K.	M	8	1	23	11	No history	Oxycephaly; blind; spastic diplegia
6	J. L.	M	9	1	44	29	No history	Speech defect; spastic diplegia
7	J. L.	M	15	5	25	13	Premature	Spastic diplegia; convulsive seizures
8	O. L.	M	15	2	?	22	No history	Spastic diplegia
9	C. M.	M	16	1	26	45	Difficult instrumental delivery	Speech defect; spastic diplegia with element of rigidity
10	W. McG.	M	10	1	32	7	No history	Cranial asymmetry; spastic diplegia; convulsive seizures
11	J. McI.	M	10	7	27	59	Difficult breech presentation; delayed animation	Speech defect; dyskinesia; spastic diplegia
12	W. O.	M	19	1	25	19	No history	Cranial asymmetry; convulsive seizures; hyperreflexia; slight spasticity of extremities
13	I. L.	F	15	1	45	7	Normal	Spastic diplegia

TABLE 20.—*Psychologic Classification of Patients with Abnormal Movements*

	Number	Percentage of Group	Percentage of Patients with Positive Neurologic Findings	Percentage of All Patients
Morons	3	23.1	1.7	0.9
Imbeciles	3	23.1	1.7	0.9
Idiots	7	53.8	4.2	2.0
Total	13	100.0	7.6	3.8

Crothers,[17] in 1921, attempted to show that lesions of the corpus striatum can explain many of the motor disorders of children. He described four syndromes that are fairly well defined: (1) double athetosis, (2) juvenile paralysis agitans, (3) progressive lenticular degeneration and (4) dystonia lenticularis (athetosis accompanied by

17. Crothers, B.: Lesions of the Corpus Striatum in Childhood, Am. J. Dis. Child. **22**:145 (Aug.) 1921.

differences in tone in various muscle groups). However, the subject of the point of origin of abnormal movements, and of athetosis in particular, has long been controversial. Bucy and Buchanan [18] described the case of a girl, aged 7, with hemiparesis, jacksonian epileptiform convulsions and athetosis, which developed following tonsillectomy and adenoidectomy. After the contralateral cerebral cortex was exposed it was found that electrical stimulation of a localized portion of the prerolandic area produced movements identical with the involuntary athetoid movements observed. The area was excised, which resulted in abolition of the athetosis and subsequent diminution in the frequency and severity of the epileptiform attacks. The conclusion was drawn that in this case the athetoid movements were effected by the area in question, which was heightened in irritability by some unknown process and possibly freed from higher inhibitory control by degeneration of transcortical connections, and that this area produced its effect by efferent impulses which passed via subcortical (extrapyramidal) centers to the spinal cord and the anterior horn cells.

The Vogts [19] expressed the belief that athetoid movements are associated with lesions of the corpus striatum. Martin [20] stated that chorea and the closely related condition of athetosis can also be established by a lesion of the body of Luys, which he considered to be the point of convergence of the striatal influence. Wilson,[21] on the other hand, thought that lesions in the "cerebello-subthalamic-thalamic cortical" afferent pathways release the effector mechanism of athetosis and of related involuntary motor activity; he also was of the opinion that the corticospinal or pyramidal pathways are the central effector mechanism of athetosis.

Foerster [22] believed that the effector mechanism is the globus pallidus, which is released by lesions of the caudate nucleus and the putamen, as shown by the Vogts. Jakob's [23] hypothesis of the pathophysiology of athetosis is essentially in agreement with that of Foerster. It is pointed out that several facts are at variance with the hypothesis of the striatal origin of athetoid movements, e. g., that athetosis is associated with evidence of damage of the pyramidal system but that so long as the hemiplegia or quadriplegia remains complete athetosis does not develop. Thus it seems that the corticospinal pathway is essential in the production of athetosis.

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18. Bucy, P. C., and Buchanan, D. N.: Athetosis, Brain **55**:479, 1932.
19. Vogt, C., and Vogt, O., quoted by Bucy and Buchanan.[18]
20. Martin, J. P., quoted by Bucy and Buchanan.[18]
21. Wilson, S. A. K., quoted by Bucy and Buchanan.[18]
22. Foerster, O., quoted by Bucy and Buchanan.[18]
23. Jakob, A., quoted by Bucy and Buchanan.[18]

The fact that athetosis and choreo-athetoid movements are so commonly observed in cases of congenital spastic diplegia, in which paralysis is seldom or never complete, makes these observations interesting and important. It must, however, be borne in mind that the muscular hypertonicity of patients exhibiting these types of abnormal movements is occasionally of a rigid rather than of a spastic type, which indicates some striatal involvement. Neither this nor the tendency of these patients to have a somewhat higher intellectual capacity than have those with purely spastic conditions has been adequately explained.

In the light of the works of Fulton, Jacobsen and Kennard,[24] and of Bucy and Buchanan [18] it would be interesting to extirpate portions of the prerolandic area in certain of these cases to observe the clinical results and to study the cellular architecture of the excised tissue. Fulton, Jacobsen and Kennard demonstrated forced grasping in monkeys following the removal of the prerolandic area.

TABLE 21.—*Patients with Tuberous Sclerosis—Composite Summary*

Case	Name	Sex	Age, Years	Order of Birth	Age of Mother	I. Q.	Character of Birth	Neurologic Status	Physical Status
1	G. B.	M	16	1	18	5	Difficult	Hyperreflexia; ankle clonus	Adenoma sebaceum; convulsive seizures
2*	N. C.	F	8	4	32	13	No history	Slight hyperreflexia	Adenoma sebaceum; convulsive seizures
3	D. D.	F	6	5	31	10	Difficult; "blue baby"	Slight spastic triplegia	Adenoma sebaceum

* The patient was recently admitted and the findings were not included in the statistical data.

Three cases of tuberous sclerosis were found in the institution.

Tuberous sclerosis is not common, and cases are rarely reported in this country. Three of our patients exhibit the physical signs and mental symptoms usually considered to be pathognomonic of that condition. Two of the patients manifest complete epiloia. The third patient does not have convulsive seizures, but the syndrome is otherwise complete.

CASE 17.—*A boy with tuberous sclerosis who manifests complete epiloia; mental deficiency of low grade, epilepsy and adenoma sebaceum.*

G. B., a white boy, aged 16, with an intelligence quotient of 5, was admitted on Feb. 23, 1923. The family history reveals no neuropathic taint. The father is living and well; the mother is alive but is said to be an invalid. There is 1 normal sibling, two years younger than the patient. Birth was difficult; instruments were used. About two months after birth a large swelling was noted in the parietal region. According to the father, a roentgenogram showed a "blood clot." The patient supported his head at 6 months but never learned to talk or

24. Fulton, J. F.; Jacobsen, C. F., and Kennard, M. A.: A Note Concerning the Relation of the Frontal Lobes to Posture and Forced Grasping in Monkeys, Brain **55**:524, 1932.

feed himself. At the age of 3 years he suddenly learned to walk. Prior to this he would remain in any position in which he was placed. After learning to walk he became increasingly more difficult to care for in the home. He had frequent and prolonged spells during which he was destructive and noisy. Commitment to an institution became necessary at the age of 6. Since his admission ten years ago, there has been little change in the mental status. The boy has from one to five convulsive seizures a month. At times he screams loudly without apparent cause. He is fairly well developed but undernourished. The head is large in proportion to the size of his body, measuring 21¼ inches (53.98 cm.) in circumference. The eyes are normal. Adenoma sebaceum, in the form of numerous small, raised, reddened papules ranging in size from that of a pinhead to that of a millet seed, is present on each cheek and extends over the bridge of the nose; on the posterior aspect of the trunk in the lower lumbar region it is present as raised, pale, fibrous, flattened, irregular papules, some of which are as large as 1 cm. in width. The heart and lungs are normal; no organs or masses are palpable in the abdomen. The genitalia are normally developed. The musculature of the extremities is flabby, but there are no gross deformities. The deep reflexes are hyperactive throughout, and there is abortive ankle clonus bilaterally. A Babinski sign cannot be elicited. Sensation is apparently normal. The patient is able to walk, but is unable to talk or feed himself and is filthy in his habits.

Critchley and Earl [25] stated that the first recognition of this special form of cerebral sclerosis, known as "tuberose" or "tuberous," is based on a few pathologic descriptions, the earliest recorded case probably being that described by von Recklinghausen [26] in 1863. Bourneville [27] is said to have been the first to recognize the condition as a pathologic entity. He noted the frequent coexistence of tumors of the kidneys of a primitive "mixed" histologic character, but the occurrence of adenoma sebaceum was for a long time regarded as a coincidence. Vogt [28] is given the credit for elucidating the clinical syndrome of mental deficiency, epilepsy and adenoma sebaceum, and Sherlock [29] for suggesting the term epiloia to connote the complete syndrome. The first abnormality to be noted is developmental delay, such as characterizes mentally defective children in general, the child failing to sit without support, crawl or walk until an unusually late age. Talking is late, and many patients with low grade mental deficiency remain mute. Cutaneous lesions make their appearance usually within the first decade and may advance somewhat abruptly at puberty. At the time of the second dentition the patient may begin to lose ground and show increasing dulness, disorderly conduct, spitefulness and emotional outbreaks. The course of epiloia is said to be rapidly down-hill after puberty, and death usually takes place

25. Critchley, MacDonald, and Earl, C. J. C.: Tuberose Sclerosis and Allied Conditions, Brain **55**:311, 1932.

26. von Recklinghausen: Verhandl. d. Berl. Gesellsch. f. Gebürtsh. **15**:75, 1863; cited by Critchley, MacDonald and Earl.[25]

27. Bourneville, quoted by Critchley and Earl.[25]

28. Vogt, H., quoted by Critchley and Earl.[25]

29. Sherlock, E. B., quoted by Critchley and Earl.[25]

in the second decade of life from cachexia, pulmonary disease or status epilepticus. There are incomplete variants of the disorder. The essential psychologic feature of epiloia is a combination of intellectual defects proper with a primitive form of psychosis; catatonia is not uncommon. The chief cutaneous lesions are the facial adenoma sebaceum on which the clinical diagnosis is frequently based.

The cerebral hemispheres are usually the sole region of the central nervous system affected, and characteristic of the disease is the presence in the convolutions of numbers of whitish, slightly prominent areas. In the walls of the third and lateral ventricles, immediately beneath the ependyma, small irregular projections are found, arising usually from the thalamus. The histologic structure of these sclerotic zones in the cortical and subependymal gray matter is described as marked anarchy in the stratification of the nerve cells, with regressive changes in the neurons themselves; considerable overgrowth of glia cells and their processes, and the appearance of curious large cells, a type foreign to the architecture of the nervous system.

The clinical variants are given as (*a*) adenoma sebaceum alone, (*b*) adenoma sebaceum with epilepsy but no mental changes, (*c*) adenoma sebaceum with symptoms of cerebral tumor and (*d*) visceral tumor alone (including retinal tumors). The etiology of tuberous sclerosis is said to be still in doubt (Critchley and Earl), but there is increasing evidence to suggest a developmental anomaly beginning early in fetal life. Critchley and Earl expressed the belief that the similarities between the condition and Recklinghausen's disease have been overemphasized.

COMMENT

It is not consistent with clinical experience and observations confirmed at necropsy or in keeping with numerous neuropathologic studies to attempt to attribute all the conditions mentioned to a single etiologic agent or process, but the aim in this study has been to attempt an explanation for certain of them and to point out a number of possible contributing factors.

Flechsig,[30] utilizing Weigert's methods of fixing and staining brain tissue, especially his stain for myelin, came to the conclusion that from a study of the myelogenesis of the different nerve systems, pathways and cerebral areas it would be possible to determine on a reliable basis the localization of psychic processes. He stated that the nerve fibers of the peripheral nerves, as well as those of the central nervous organs, form their myelin sheaths in a strictly systematic fashion from the standpoint of time, and he delineated three principles which must be

30. Flechsig, Paul: My Myelogenetic Brain Theory, translated by Bernard J. Alpers, private distribution.

differentiated in this connection: 1. Similar nerve fibers, that is, nerve fibers inserting in like manner, receive their myelin simultaneously, and dissimilar systems, in a systematic manner under the influence of gradations of time. 2. The formation of the myelin carries with it the first anlage of the axis-cylinders from the neuroblasts (Flechsig, His). 3. Myelogenesis repeats the phylogenesis of the entire nervous system, in accordance with the biogenetic principle of E. Haeckel. Flechsig considered it significant that the myelin does not form at once along the entire length of a fiber, at least not in the very long tracts, such as the pyramidal tracts, where the myelin is pushed gradually downward from the cortex. He also mentioned an observation made by Held, who showed experimentally that illumination of the eye hastens the deposit of myelin in the optic nerves. This fact is important, since it helps to explain the favorable results obtained with early physical training. He indicated further an observation made by His Sr. in a 6.9 mm. embryo, in which he demonstrated the outgrowth of neuroblasts in the nuclei of the motor nerves and found the hypoglossal nerve and its cells of origin particularly well developed. He considered the hypoglossal nerve to be the earliest motor cranial nerve to develop and phylogenetically one of the oldest structures, and pointed out its great importance in life. This view appears consistently correct when one traces the motor patterns in the normal child from birth to the period at which he has full motor control, because it is seen that there is a regular progression of development and achievement. The child is born equipped to perform only those functions necessary to begin and sustain life. He starts to breathe in response to external stimuli and can perform the necessary suctorial and deglutitive movements, which accomplishments are common to the normal and the abnormal child alike. At this stage children destined to have congenital spastic states are seldom recognized as being abnormal, and it is not until later, when they should have progressed farther along the road to normal motor control, that it is discovered that some factor is retarding development. Those who remain almost completely spastic and those who may manifest only a persistent extensor response to plantar irritation as evidence of interference in the development of the pyramidal tracts vary widely as regards the stage at which "orderly progression" stops. Here it may be well to call to mind that in the majority of patients suffering from congenital spastic diplegia, even in those in which the condition is thought to have been related to birth, the most marked manifestations of the disease are observed in the lower extremities, and that no patients have been observed in whom the arms alone have been involved. Furthermore, the facial muscles are seldom spastic, and practically all patients can swallow without difficulty, although a few cases are seen in which food must be placed far back on the tongue or in the

pharynx to bring about the swallowing reflex. In striking contrast are those patients who show monoplegia or hemiplegia and whose intellectual level is usually somewhat higher than that of the diplegic or paraplegic patient. In their cases we believe that the condition is more likely to be the result of trauma at birth. But even in these cases it is difficult to accept the theory of trauma at birth as being solely responsible for the condition. For example, in this series of patients there is a group of siblings, 2 boys and a girl, all of whom are mentally defective. Two of the siblings have hemiparesis; the other is without neurologic signs. There is no history of injury at birth for any of the 3, and they are all the offspring from the mother's first marriage; an offspring from her second marriage is normal.

When it is noted that most patients with congenital spastic paralysis are in addition mentally deficient, it appears that cells and pathways other than those constituting the motor system are involved, and this is borne out by observations concerning the relationship between the degree of intellectual impairment and the motor defect. The main sensory pathways cannot be implicated in the process, as they are apparently fully myelinated at birth, and sensation is rarely found impaired in cases of congenital spastic diplegia. If a defect in myelogenesis of the pyramidal tracts is responsible for the motor phenomena, it may be safely postulated that a similar defect in the development of the association pathways may account in a measure for the intellectual impairment. There is some support for such a point of view in the results of studies on myelogenesis of the cerebral cortex by Flechsig,[30] who has shown that the intracortical association systems develop their myelin sheaths, for the most part, very late, suggesting that the degree of psychic capacity at different ages parallels the intracortical process of development. That gross hemorrhage overlying the cortex, resulting from trauma at birth, could produce these symmetrical conditions does not seem logical. On the other hand, petechial hemorrhages beneath the ependyma of the ventricles and scattered throughout the cortex and basal ganglia *may be* important etiologic agents in producing uniform disturbances bilaterally. That these hemorrhages may be related to a defect in myelogenesis may be explained, as has been pointed out by Patten and Alpers [31] and others, by the fact that such hemorrhages lie within the germinal foci of neuroblasts and spongioblasts in the periventricular areas from which arise the cells that are intimately related to the production of myelin. The cause for the occurrence of such petechiae has not been defined, but theoretically they may be considered as attributable to defects of development in utero.

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31. Patten, C. A., and Alpers, B. J.: Cerebral Birth Conditions with Special Reference to the Factor of Hemorrhage, Am. J. Psychiat. **12**:751 (Jan.) 1933.

CHARACTER OF BIRTH

In an attempt to evaluate the importance of the factor of trauma at birth in the production of the neurologic conditions observed, the cases were reviewed from the standpoint of difficult and normal labor. The findings are summarized in table 22.

The figures for the two groups are much the same. Only one third of the patients with available histories who show lesions of the pyramidal or extrapyramidal tracts have a history of difficult birth. In the remaining two thirds of the cases birth was considered normal. A history of difficult birth was obtained for almost as many neurologically normal patients as those with definite neurologic conditions, in spite of the general tendency to consider trauma at birth as the most important etiologic factor in the production of spastic palsies in general. These figures tend to minimize the importance of trauma at birth as a cause of congenital spastic palsy. In Patten's [32] series of 46 cases of spastic diplegia a somewhat higher percentage of patients had a history of difficult birth. Levinson and Saphir,[33] in a study of 45 cases of intracranial hemorrhage in the new-born, found a striking lack of cellular reaction in the meninges and concluded that the small number of clinically evidenced complications of intracranial hemorrhage in children who survive can be explained by the absorption of the hematoma without organization and without the formation of a fibrous scar. In 3 instances in their series of cases intracranial hemorrhage occurred in an infant delivered by cesarean section, indicating that trauma was not the principal cause of the hemorrhage; maternal toxemia was thought to be an etiologic factor.

TABLE 22.—*Relation of Neurologic Conditions to Difficult or Normal Labor*

	History Available	Difficult Birth	Normal Birth
Group with positive neurologic findings...	85	30 (35.3%)	55 (64.7%)
Group with normal neurologic findings....	81	24 (29.6%)	57 (70.4%)
Total.....	166	54 (32.5%)	112 (67.5%)

ADDITIONAL FINDINGS OF CLINICAL INTEREST

Only 7 of the patients in this series have positive Wassermann reactions of the blood, and in 2 of these the reaction is doubtful. These patients constitute 2 per cent of the entire group, but in no instance can

32. Patten, C. A.: Cerebral Birth Conditions with Special Reference to Cerebral Diplegia, Arch. Neurol. & Psychiat. **25**:453 (March) 1931.

33. Levinson, A., and Saphir, O.: Meninges in Intracranial Hemorrhage of the New-Born, Am. J. Dis. Child. **45**:973 (May) 1933.

we state positively that syphilis is the sole cause of the mental defect. Myerson [34] recently stated:

> While it cannot be doubted that syphilis causes alterations of the brain, and thus produces dementia both in the adult and in the child, there is no proof at present that syphilis causes feeble-mindedness. There is nothing in the general appearance and the general reactions of the congenital syphilitic feeble-minded to distinguish them from the mass of the feeble-minded. Therefore, there is ground for the assertion that, at the present time, we can safely state that syphilis of ancestors causes little, if any feeble-mindedness in descendants.

Potter pointed out that juvenile dementia paralytica may be manifested only as hypophrenia, but there are no similar examples in this series.

TABLE 23.—*Psychologic Classification of Patients with Mongolism*

	Number	Percentage of Group	Percentage of All Patients
Morons	1	3.22	0.2
Imbeciles	13	41.94	3.7
Idiots	17	54.84	4.9
Total	31	100.00	8.8

TABLE 24.—*Incidence of Mongolism According to Age Groups*

Mother's Age at Time of Patient's Birth	Number of Patients
Under 20 years	3
20 to 29 years	6
30 to 39 years	13
40 to 49 years	9
50 years or over	1

In the course of this study, 17 persons with mongolism were examined, and the records of 15 others were reviewed. One patient died before a psychometric examination could be carried out. Only 2 patients in this group present neurologic signs, one having a positive Babinski sign bilaterally without other evidence of involvement of the pyramidal tract, and the other having spastic diplegia.

In the cases reviewed the most striking feature noted was that a large proportion of the patients with mongolism were born late in the mother's child-bearing period. This is brought out clearly in table 24. These figures are important when compared with figures quoted for the general population. Birth statistics of the United States Census Bureau for 1927 show the medium age of mothers at the birth of the first child to be between 21 and 22 years, while the largest number of first births at any one age was at 19 years. The statistical bulletin of the Metro-

34. Myerson, Abraham: Nature of Feeble-Mindedness, Am. J. Psychiat. **12:** 1205 (May) 1933.

politan Life Insurance Company for September 1930 shows that the median age for mothers at the birth of the first child was 23 in 1920 (Doll,[5] p. 69).

Jenkins,[35] in considering the etiology of mongolism, stated that any familial tendency is extremely slight and pointed out that in the case of dizygotic twins only one member of a pair is affected, while in that of monozygotic twins both are affected. The incidence of the condition is said to increase in relation to advancing maternal age, and it is much more likely to occur in children born to mothers late in the child-bearing period. Jenkins [35] considered the relation between the incidence of mongolism and the age of the father as merely a result of the correlation between the ages of the parents, and he expressed the belief that the condition results from diminished viability of the ovum. Our figures tend to support Jenkins' hypothesis. Certainly it is more than a coincidence that the mothers of 23 of our 32 patients with mongolism were 30 years of age or older at the time of the births.

Waring [36] expressed the belief that mongolism is due to a defect in the individual germ plasm and is not the result of general physical enfeeblement in the parents. The fact that mongolism occurs in one of dizygotic twins he considers as further evidence of this view.

CONCLUSIONS

A neurologic survey of 350 feebleminded patients has shown that neurologic defects in patients with hypophrenia are probably more frequent than is generally believed. Naturally, the percentages here reported cannot be applied to the total feebleminded population, as they are based on the types of patients who must be confined to an institution and who therefore belong largely in the idiot and imbecile groups.

Nothing was found in the group with positive neurologic findings which would distinguish the character of the mental defect from that noted in the neurologically normal group. This, it seems, indicates that mental deficiency, by and large, probably has a somewhat uniform pathology, and that the occurrence of neurologic defects is but a manifestation of a more extensive developmental defect.

No mental or neurologic manifestations were found in the whole group which would in any manner clearly indicate trauma at birth as a certain etiologic factor, as patients with a history of normal labor presented the same types and intensity of symptoms as those with a history of difficult labor. Undoubtedly, cerebral injuries occur during difficult labor and from instrumentation, but they probably result more fre-

35. Jenkins, R. L.: The Etiology of Mongolism, Arch. Neurol. & Psychiat. **28**:1228 (Nov.) 1932.

36. Waring, J. I.: Mongolism in One of Twins, Am. J. Dis. Child. **41**:351 (Feb.) 1931.

quently in monoplegia or hemiplegia and less often in a disturbance of intellect. In addition, there are undoubtedly cases of primary congenital defect in which injury is sustained during labor and which might erroneously be classified too strictly in one or the other group; consequently, any conclusions reached must be guarded.

It is stated that there are occasional cases of cerebral diplegia in which intellectual development is normal; this is used as an argument against the theory of the etiologic importance of a developmental defect of prenatal origin. To us these exceptional cases do not invalidate the theory or the significance of congenital failure of development. It seems to us that it is possible that myelin formation may be irregular in distribution and that the association fibers in the cerebral cortex may become fully myelinated while those of other systems do not. If this is so, there *should* be cases of spastic diplegia associated with a higher level of mental development. Following Flechsig, and at the same time recognizing the need for further scientific investigation from this standpoint, the stimulation to myelin sheath formation comes, at least in part, from the functional activity of contiguous structures or phylogenetically related systems. In cases in which the striatal system alone is involved it would be natural to suppose that the corticospinal pathways were normally myelinated and functionally active; this would favorably influence the association fiber development in the cortex and produce a more normal degree of mental equipment. In cases in which corticospinal failure of development is marked, it must be assumed, contrariwise, that motor development has nearly ceased at the level of the midbrain and that, if the defect is in myelogeny, the cortical association fibers which are the last to myelinate will possibly fail to develop and function. Possibly therein lies in part an explanation for ordinary feeblemindedness—a markedly incomplete association fiber equipment.

SUMMARY

In 82.6 per cent of 350 patients examined the intelligence quotient is below 50.

Approximately 50 per cent of all the patients show definite neurologic symptoms and signs.

Twenty-two and three-tenths per cent of the neurologically normal patients are classified psychologically as morons, in contrast to 12.3 per cent of the patients with positive neurologic findings. In other words, there are approximately twice as many patients with the higher intelligence ratings in the group showing no neurologic signs.

Epilepsy is much less common in the neurologically normal group, 16.1 per cent of the patients in this group having this condition, as compared with 36.2 per cent in the group with positive neurologic findings.

In only 4.2 per cent of the patients observed are the neurologic conditions postnatal in origin.

There is a general correlation between the intellectual level and the degree of neurologic involvement, patients who show most marked spasticity and other organic signs rating lowest in the psychometric tests.

Trauma at birth of a gross type cannot be ascribed as the cause of any appreciable number of the neurologic conditions observed, but the part played by pressure at birth resulting in anoxemia needs further investigation.

Eight patients have neurologic conditions which may possibly be related to trauma at birth, although another etiologic explanation has been suggested in the conclusions.

Twenty-four patients have hyperreflexia and a Babinski sign without spasticity. The incidence of epilepsy is high in this group, and it appears that the sequelae of convulsive disorders may account for the neurologic signs observed in certain of these patients.

All our patients with hydrocephalus exhibit signs of involvement of the pyramidal tracts, but in spite of marked interference with the motor pathways they have, in most instances, intelligence quotients above the idiot level.

The fact that mental deficiency occurs with and without neurologic complications is presumptive evidence of structural defects related to failure of evolution in intra-uterine life.

Syphilis cannot be held to play a large rôle in the production of either neurologic abnormalities at birth or feeblemindedness.

There appears to be a definite relationship between the age of the mother and the incidence of mongolism, the incidence increasing with advancing maternal age.

Three patients with tuberous sclerosis are included in the group studied.

CERVICODORSAL SYMPATHECTOMY IN MULTIPLE SCLEROSIS

ITS RATIONALE AND REPORT OF EIGHT CASES

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Not since multiple sclerosis was first recognized as a disease entity has a treatment for the condition been of permanent value. Practically everything that has been done has resulted in temporary relief and has been aimed at causing arterial dilatation. It is my purpose to call attention to a method which causes dilatation of the cerebral vessels which is probably permanent, and which may secondarily relieve constriction of the vessels of the spinal cord. The various phases of the symptomatology of the disease will not be discussed. My main endeavor will be to explain the rationale of cervicodorsal sympathectomy as applied in the treatment for this disease.

Undoubtedly, the exact etiologic factor underlying the formation of the sclerotic plaques in multiple sclerosis remains to be determined. Most authorities have suggested that some acute insult to the nerve tissue may cause the onset of the disease. The nature of this insult, it has been stated, is usually a form of toxemia—incident to an acute infectious disease or possibly to metal poisoning. Others have traced the beginning of the symptoms to injury, to a fall or to a blow on the back. Nevertheless, in about 50 per cent of cases no etiologic factor can be determined.

Whatever the irritation may be, accumulated clinical evidence in the cases here presented suggests that the sympathetic nervous system is the recipient of stimuli which are capable of exciting activity in this system. It is reasonable to assume that one set of sympathetic nerve fibers may be more liable to insult than another, thus being more susceptible to stimulation. This, of course, is known to be a fact when the system is considered in the light of such diseases as hyperthyroidism and Raynaud's and Hirschsprung's disease. The somatic nervous system may also be attacked in part, for example, the radial nerve in cases of lead poisoning.

These statements are made in view of the evanescent quality of the symptoms early in the disease and the possibility that this charac-

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teristic may be due to the sudden formation of sclerotic plaques in certain areas in the central nervous system, which disappear only to reappear in other areas.

This assumption is based on the newer conception of the circulation in and around the plaques.[1] Attention has been called to these changes in a previous article which contains a report on the results of cervicodorsal sympathectomy in a case of multiple sclerosis.[2]

Briefly, the changes which occur in the cerebral circulation seem to be due to vasoconstriction, with an ensuing decrease in the blood supply. This decrease may be the basic, causative factor of ischemia, with its resulting anoxemia, the end-result of which is irritation. It has been assumed that the irritation may act on a vasomotor center, on centers in control of the sympathetic nervous system in the hypothalamus or even on centers in the frontal cortical area.[3] Experiments have shown that sectioning the sympathetic nerve fibers which supply the impulse of vasoconstriction to the cerebral vessels results in a definite betterment of the blood supply.[4] The more normal functioning of the extremities observed following the operation is probably due in great measure to the relief of the spasticity. This, too, may be traced to relief of irritation in the pyramidal tracts.

In rationalizing the procedure, it might be assumed that with an increase in the blood supply there follows regeneration of the demyelinated areas and possibly reduction in the glial proliferation. Such a process would explain the more normal conduction of impulses following the operation.

Why do remissions occur spontaneously in cases of multiple sclerosis? Is it possible that, whatever the irritating factor is in the individual case, either the irritation ceases for the time being or the sympathetic nervous system acquires a resistance to the irritation, thus allowing it again to function normally for a time?

If this premise is correct, the end of a period of remission signifies that either one or the other of the aforementioned factors has begun to manifest itself. The patient, of course, still has the same sympathetic nervous system, and in the great majority of cases it will still be susceptible to an insult which would not upset a more normal system.

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1. Putnam, T. J.: The Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, New England J. Med. **209**:786 (Oct. 19) 1933.

2. Wetherell, F. S.: Multiple Sclerosis: Cervicodorsal Sympathectomy as a Relief Measure, J. A. M. A. **102**:1754 (May 26) 1934.

3. Linell, E. A.: The Autonomic Nervous System: A Sketch of Its Structure and Functions with a Consideration of Its Cerebral Connections, Am. J. Psychiat. **13**:925 (March) 1934.

4. Royle, N. D.: The Surgical Treatment of Disseminated Sclerosis, M. J. Australia **1**:586 (May 13) 1933.

The fact that the majority of persons with multiple sclerosis have recurrent exacerbations seems to indicate that the latter statement is true.

It is well known that peripheral arterial disease, treated by sympathectomy, responds excellently, provided the vessels are still inherently capable of dilatation. In some instances, however, in which dilatation is possible only in a minor degree, results have been obtained by an increase in the collateral circulation following sympathectomy. As the main vasomotor supply to the cerebral vessels emerges by way of the inferior cervical and first thoracic ganglia, it is reasonable to assume that as a result of sectioning these fibers there is a change in the blood supply of the brain, which results in a more normal rate of blood flow to, and a more normal nourishment of, the parts affected.

Acute asphyxia, such as may be obtained by tying off the vessels to the brain, rapidly results in destruction of nerve cells. This occurs in the course of minutes. If a gradual and continuous decrease in the blood supply results because of the constrictor activity of vasomotor fibers to cerebral vessels, is it not reasonable to assume that damage may occur as a result of the slower process?

In the following case histories the striking feature is the almost immediate amelioration of some of the physical disabilities. In each instance the possibility that the changes which took place may have been a postanesthetic effect has been taken into consideration, but the continued improvement long after such effects could be active militates against such a conclusion. Furthermore, the improvement noticed at first has in each instance been continued up to the time of this report. It is true, of course, that the patient and those attendant on him after his return home have constantly attempted movements of the various muscles, and this constant attention and the effort put forward toward improvement are undoubtedly a helpful factor. Nevertheless, it does not seem possible that in each of eight successive cases the improvement was due to a natural remission. It is my hope that the clinical evidence presented in the following histories will stimulate further research into this problem from the standpoint of the sympathetic nervous system. The cases which are here cited have all been checked by neurologists.

REPORT OF CASES

CASE 1.—H. M., a woman aged 38, who had been ill for eight years, complained chiefly of inability to walk and to feed herself.

Examination gave the following results:

Signs and Symptoms	Degree
Fatigue and weakness	Marked
Stiffness of the upper extremities	Moderate
Stiffness of the lower extremities	Marked
Difficulty in walking	Unable to stand

Signs and Symptoms	Degree
Eyes: Nystagmus	None
Bitemporal pallor	None
Vision	Poor
Lids	Continual blinking
Ataxia of the upper extremities	Marked
Ataxia of the lower extremities	Marked
Defect in speech	Slight scanning
Facial nerve	Normal
Deviation of the tongue	None
Disturbance of deglutition	Slight
Emotional instability	Moderate
Remission of symptoms	None
Pain, touch, temperature disturbance	None
Vibratory sensation	None
Rectal disturbance	Constipation
Bladder disturbance	Retention
Mental changes	None
Auditory nerve	Normal
Muscle atrophy	Slight, in the legs
Intention tremor	Marked
Dizziness	Moderate
Reflexes: Oppenheim	Present
Gordon	Present
Abdominal	Absent
Patellar	Marked exaggeration
Clonus	Inexhaustible
Babinski	Present
Romberg	Not ascertained

Cervicodorsal sympathectomy was performed on April 2, 1934, and the improvement up to May 15 was as follows: The patient was able to feed herself. There was marked diminution of the ataxia, and she walked with assistance. Catheterization was performed seven days after operation and was followed by incontinence with no overflow. There was a gradual return of fairly normal function of the bladder, catheterization being done only occasionally. The patient was less nervous and much happier. There was less blinking of the eyelids, and her body felt stronger. She was less dizzy and was able to sit up in a chair for a longer period each day. The patellar reflexes were less active. The ankle clonus was exhaustible on the left side and nearly absent on the right.

CASE 2.—A. C. B., a woman aged 27, who had become ill sixteen years before the present examination, complained chiefly of difficulty in walking, twitching of the muscles, and difficulty in speech.

Examination gave the following results:

Signs and Symptoms	Degree
Fatigue and weakness	Moderate
Stiffness of the upper extremities	None
Stiffness of the lower extremities	Slight
Eyes: Nystagmus	Present
Palsies	None
Bitemporal pallor	Present
Vision	Normal
Ataxia of the upper extremities	Marked
Ataxia of the lower extremities	Slight
Facial nerve	Normal
Defect in speech	Scanning, explosive
Deviation of the tongue	None
Disturbance of deglutition	Slight
Emotional instability	Moderate
Remissions of symptoms	Several
Pain, touch, temperature disturbance	None

Signs and Symptoms		Degree
Disturbance of vibratory sensation		None
Rectal disturbance		Constipation
Bladder disturbance		Retention
Mental changes		None
Auditory nerve		Normal
Dizziness		None
Muscle atrophy		None
Intention tremor		Present
Reflexes:	Oppenheim	Absent
	Gordon	Absent
	Abdominal	Absent
	Patellar	Exaggerated
	Clonus	Absent
	Babinski	Absent
	Romberg	Absent

Cervicodorsal sympathectomy was performed on Feb. 14, 1934, and the improvement up to April 30, was as follows: During the month the patient was in the hospital there was gradual improvement, particularly in speech and in the tremor of the hands. She walked several steps alone at the end of three weeks. The ataxia of the lower extremities was definitely improved. Two months after operation the patient's physician stated: "She is depressed for a day or two every few weeks, and at that time she is unable to walk as well, requiring an attendant. At other times she is able to walk alone." Her writing was much improved.

The hysterical element in this case was a disturbing feature. Generally, the patient's condition was much better than before the operation.

CASE 3.—L. H., a man aged 36, who had been ill for eight years, complained chiefly of inability to walk. Examination gave the following results:

Signs and Symptoms		Degree
Fatigue and weakness		Marked
Stiffness of the upper extremities		Absent
Stiffness of the lower extremities		Slight
Eyes:	Nystagmus	Marked
	Palsies	Absent
	Bitemporal pallor	Present
	Vision	Poor, blurring
Ataxia of the upper extremities		Marked
Ataxia of the lower extremities		Marked
Defect in speech		Scanning
Facial nerve		Normal
Deviation of the tongue		None
Disturbance of deglutition		Occasional
Emotional instability		Moderate
Remission of symptoms		Several
Pain, touch, temperature disturbance		None
Vibratory sensation		Normal
Rectal disturbance		Constipation
Bladder disturbance		Retention
Mental change		Moderate
Auditory nerve		Normal
Muscle atrophy		None
Intention tremor		Moderate
Dizziness		Slight
Reflexes:	Oppenheim	Present
	Gordon	Present
	Abdominal	Absent
	Patellar	Exaggerated, plus
	Clonus	Bilateral inexhaustible
	Babinski	Present
	Romberg	Present

Cervicodorsal sympathectomy was performed on Feb. 3, 1934, and the improvement up to May 15, was as follows: The patient was markedly depressed for one month after operation. He was treated by Dr. Boudreau, a psychiatrist, and was entirely relieved. He walked a dozen steps with the assistance of his wife, and he was able to feed himself. His speech was distinct, and his eyesight was markedly improved. The ankle clonus disappeared for two months; there was an occasional recurrence, but it was very weak. The Babinski sign was absent. The patient felt stronger every week. The bowels functioned normally. There was motion in the legs about two weeks after operation, beginning with the extensor quadriceps muscles. The control of the bladder was normal.

Case 4.—Mrs. J. W., aged 63, who became ill fifteen years before the present examination, complained chiefly of dizziness and difficulty in walking.

Examination gave the following results:

Signs and Symptoms		Degree
Fatigue and weakness		Marked
Stiffness of the upper extemities		None
Stiffness of the lower extremities		Marked
Difficulty in walking		Marked
Eyes: Nystagmus		Marked
Palsies		None
Ataxia of the upper extremities		Marked
Ataxia of the lower extremities		Marked
Spastic gait		Marked
Scanning speech		Marked
Facial nerve		Normal
Deviation of the tongue		None
Disturbance of deglutition		None
Emotional instability		Marked
Remission of symptoms		Yes
Pain, touch, temperature disturbance		Marked
Vibratory sensation		Absent
Rectal disturbance		None
Bladder disturbance		None
Mental changes		None
Auditory nerve		Normal
Muscle atrophy		None
Intention tremor		Marked
Reflexes:	Oppenheim	Absent
	Gordon	Absent
	Abdominal	Absent
	Patellar	Very active
	Clonus	Absent
	Babinski	Absent
	Romberg	Sways

Cervicodorsal sympathectomy was performed on Jan. 17, 1934, and the improvement up to February 10 was as follows: The patient experienced no dizziness for the first time in fifteen years. She was able to feed herself better. There was less tremor of the hands. The blood pressure, which was 170 systolic before operation, remained from 40 to 50 points lower for four weeks after operation. (It returned to 170 systolic in two months.) The patellar reflexes were less active, and the ataxia of the extremities was less. There was less nystagmus, and vision had improved.

On May 15, the patient walked much better and alone. The improvements previously reported have increased. A letter from the patient stated that she felt better in all respects and both she and her family were pleased with the progress.

Vibratory sensation was present.

CASE 5.—R. E., a man aged 57, was operated on in 1933; the case has previously been reported.[2] At the time of writing the patient continues to show improvement; he was able a month ago to take a trip of several hundred miles to visit a relative. He seems well pleased with his ability to get about and to handle himself in ways which had been impossible for years.

CASES 6, 7 and 8.—The cases of three patients who were operated on within a few weeks and are still in the hospital will not be reported on in detail at this time, although in each instance certain improvements have already taken place. One man, aged 30, called attention five days after the operation to the fact that he was able to raise both legs from the bed, which he had been unable to do before the operation. This man also had had an inexhaustible ankle clonus on the right side; five days after operation the ankle vibrated about twelve times and then stopped. The ankle clonus on the left side, although not inexhaustible before operation, showed a marked lessening in intensity.

The second patient, a man aged 57, one week after operation called attention to the fact that he was able to reach over to a window sill and pick up his pipe with one hand and bring it over to and grasp it with the other hand without a trace of tremor or shaking. This, he stated, had given him a scare when he first noticed that he could do it, because of his previous difficulty in handling the pipe and his fear that he might shake burning tobacco on the bedclothes.

The third patient, a woman aged 46, stated that her legs felt stronger and her speech was much clearer. The improvement in speech had been noticed by attendants.

These last three cases will be reported in a subsequent communication when enough time has elapsed to evaluate the improvement properly.

OPERATION

Cervicodorsal sympathectomy consists of removing the inferior cervical and the first thoracic ganglion by the posterior approach. The transverse process of the first thoracic vertebra and about 1 inch (2.5 cm.) of the first rib are removed. The ganglia are picked up, and the cords above and below are sectioned, as are all the rami, and the structures thus sectioned are removed. The operation has been described in detail by Henry.[5] There has been no fatality in this series. With the exception of the first case, bilateral sympathectomy has been done in one stage. General anesthesia with nitrogen monoxide and ether has been used in each instance; all patients have had little postoperative discomfort and have stood the procedure exceptionally well.

SUMMARY

The operation of cervicodorsal sympathectomy is proposed as a measure of relief in cases of multiple sclerosis.

An attempt is made to rationalize the procedure on a basis of betterment of cerebral circulation, which may relieve irritation and allow a more normal blood supply and more normal conduction of nerve impulses.

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5. Henry, A. K.: Exposures of Long Bones and Other Surgical Methods, New York, William Wood & Company, 1927.

Cases are presented in which there was improvement in various symptoms that had been present before the operation.

On the basis of the improvement shown in these cases, the plea that multiple sclerosis may respond even better if earlier operation is resorted to is made.

Further investigation as to the relation of the sympathetic nervous system to this disease seems to be indicated on the basis of the clinical results after sectioning of the cervicodorsal sympathetic cord and ganglia with the rami.

ABSTRACT OF DISCUSSION

DR. NOBLE R. CHAMBERS, Syracuse, N. Y.: Not so long ago most neurologists associated multiple sclerosis with Charcot's triad of nystagmus, scanning speech and intention tremor. It seems needless to say that it is now known that this picture is seen only late in the disease and that the competent observer may diagnose multiple sclerosis before any of the triad appears, perhaps from a transient spasticity or from bitemporal pallor, the optic signs often appearing first.

Concurrently with efforts to recognize the disease in its earliest stages, much research has been conducted as to the etiology and the treatment of the condition. Many theories have been advanced as to the cause, it being suggested even that the disease is due to a spirochete. Many forms of treatment have been suggested: antisyphilitic therapy, injection of foreign protein, fever therapy, and, more recently, the administration of quinine, as advocated by Brickner of New York. There have been some favorable results from the use of quinine in my experience, but progress has been slow, and I was not sure whether a period of remission, so characteristic of the disease, was not occurring.

The important point from a pathologic standpoint is that there is degeneration of the myelin sheaths and that there are, at least in the early stages, many axons intact. It is not necessary to discuss the differential diagnosis before this group.

For many years the autonomic nervous system has been a subject of interest and research and a baffling one. It is known that this system innervates the circulation, the internal organs, the sweat glands, the hair, etc., and that it is closely connected with the endocrine system. Through the work of Cannon and others it has been learned that the emotions have a great influence on the autonomic nervous system. The surgical work of Royle and others has contributed knowledge concerning this system. Any psychiatrist knows its extreme importance in the psychoneuroses, and how does one know that it is not a potent factor in the so-called functional psychoses? The psychoneuroses are treated by sedatives, endocrine preparations and measures directed toward altering the emotional content of the patients' lives, but when one sees a case of multiple sclerosis one is baffled, as I have tried to point out, although an ardent analyst might find psychic factors in the patient's early life.

I believe that there is definite hope in the use of cervicodorsal sympathectomy. I base this belief on the cases of several patients whom I have had the privilege of examining for Dr. Wetherell. The improvement has been striking and so closely connected with the surgical procedure that I cannot consider it a natural remission. Every one will agree that relief from symptoms is always of value, but that relief directed toward the etiologic factor is of more value. At first sight, cervicodorsal sympathectomy may seem to give relief from symptoms, but I believe that in cases of multiple sclerosis there is a great possibility that the

patient is unduly sensitive to vasoconstrictor stimuli and that the operation advocated by Dr. Wetherell is really directed toward the etiologic factor, causing as it does permanent vasodilatation.

The work of Harvey Cushing is well known, and recently work has been done by Stanley Cobb on the cerebral circulation (*Am. J. Psychiat.* **13**:947 [March] 1934) and by Eric Linell on the autonomic nervous system (*Am. J. Psychiat.* **13**:925 [March] 1934).

I do not believe that Dr. Wetherell has at any time been overenthusiastic but has insisted that a diagnosis of multiple sclerosis be made without reservation. He has proceeded with true scientific conservatism.

DR. GEORGE B. HASSIN, Chicago: The rôle the blood vessels are supposed to play in the causation of the plaques and other changes in the central nervous system in cases of multiple sclerosis is greatly exaggerated. One may find extensive foci of degeneration in the brain and the spinal cord without demonstrable changes in the blood vessels. If changes in the walls of the blood vessels are present, such as dilatation of their adventitial spaces, which are filled with fat granule bodies, hyperplasia and consequent thickening of the adventitial layer, they are secondary and not essential.

Even if it were possible to improve the blood supply by sympathectomy, it would not be possible to bring about regeneration of the destroyed myelin, for the central nerve fibers do not regenerate, especially in adults, nor is it possible to cause absorption of the plaques, for as these are scars they cannot undergo further changes. However, multiple sclerosis is such a distressing, hopeless condition that any therapeutic measure that appears promising should be given careful consideration, regardless of the difference of opinion as to the pathophysiologic features of this disease.

DR. TEMPLE FAY, Philadelphia: I do not feel particularly qualified to discuss this subject from the standpoint of any surgical observations similar to those reported, but I have two observations that I believe bear out what has been noted this morning. I have placed a little different interpretation on them, although perhaps my result is the same, for I feel that one can check the progressive course of multiple sclerosis if one goes back to fundamental principles and attempts to improve the blood supply to the cerebrum and the spinal cord.

If one is treating a bedsore (which is a chronic, degenerating process, with known causes of pressure and lack of circulation), certainly one favors in every sense a return of circulation in order that there may be repair of tissue and prevention of further damage. One cannot bring back the structures in the spinal cord and the brain that have been lost, but by improving the circulation to the brain and the spinal cord one may prevent further loss and perhaps give back some function to those cells that are still present but unable to manifest their actual physiologic nervous mechanism.

I have been struck by encephalographic findings indicating large areas in the brain that have undergone atrophy, and for some reason these have been rather well localized to the parietal region. They are such characteristic and picked-out areas that I have been wondering if there may not be some association between the characteristic symptoms and this selective loss of brain substance. The pathologic changes in the spinal cord which Dr. Hassin and other neuropathologists have so clearly pointed out are, of course, extensive in cases of multiple sclerosis.

My associates and I have obtained remarkable results in two cases by the use of spinal drainage and dehydration similar to the treatment that we have been using in cases of epilepsy and following, with the idea of increasing the blood

supply in the craniovertebral cavity. The first patient was willing to try the experiment. Certainly spinal drainage has helped during the past three years, for the patient had been bedfast and following the drainage she went back to teaching and for the last year and a half has not even used a cane. She has returned occasionally for spinal drainage. We were able to maintain dehydration with 20 ounces (580 cc.) of fluid a day and a dry diet. The second patient also improved. Putnam noted the value of spinal drainage. We have merely prolonged the good results by adding dehydration.

I believe that all we did was to improve the nutrition by increased circulation to the affected part, thus preventing further degeneration. This may be called a temporary "remission." I am not willing until five years have passed to make an analysis of the possibility. We did what we should have done in the case of a bedsore, that is, attempted fundamentally to improve the blood supply.

I believe that this paper is of extreme importance. It at least offers a procedure to check or to assist the process of degeneration. The condition is not yet understandable, and certainly until it is one is not going to cure it.

Dr. Henry R. Viets, Boston: Some dysfunction of the vascular supply of the central nervous system has long been considered as an etiologic factor in multiple sclerosis. Many investigators have attempted to produce the lesions experimentally by altering the arterial blood supply to the central nervous system.

More recently, a fine piece of investigative work has been done by Dr. Tracy Putnam, who has turned from the arterial side to the venous side of the problem. He has shown, by causing thrombosis in the smaller venules of the central nervous system, that areas of degeneration are formed which are almost similar to the plaques seen in disseminated sclerosis. This work, I think, is of great interest, and it may lead to a new conception of the etiology of this disease.

Does Dr. Wetherell feel that as a result of his operative intervention there are changes in the venous return of blood from the nervous system which might in some way stimulate recovery? Could dilatation of the venous system, perhaps suggested by Dr. Putnam's work, be a factor as well as the changes in the arterial system?

Dr. W. James Gardner, Cleveland: As an indirect method of observing the changes in the cerebral circulation which may accompany an interruption of the sympathetic nerves to the head, I have on a few occasions injected procaine hydrochloride into the cervicodorsal sympathetic ganglion with a lumbar puncture needle connected to a manometer. This procedure has shown that as soon as the physiologic effects of the injection become apparent, there is an increase in the cerebrospinal fluid pressure of approximately 40 mm. of water. This, I assume, in the absence of definite changes in the blood pressure, is due to an increased volume of blood within the cranial cavity.

I should like to ask Dr. Wetherell whether or not any histopathologic studies were made on the ganglia which he excised.

Dr. A. S. Crawford, Detroit: Progress has been made and is now being made in the furtherance of the knowledge of the nervous system by the combined study of the surgeon, the anatomist and the physiologist. As this interesting history is traced through the last few years, one sees how daring the surgeon has been in starting off on a practically uncharted course.

It was my privilege to be with Dr. Adson at the time that sympathectomy was first introduced after the work of Royle and Hunter, and at that time we looked ahead and saw opening up all sorts of possibilities. Fortunately, all possible types of diseases were not treated at that time, but the most likely conditions were

treated first. Brilliant results have already been obtained in the treatment of Raynaud's disease and other conditions due to vasoconstriction. The treatment of multiple sclerosis was put in the background to be tried later.

I think that Dr. Wetherell should be definitely commended for going ahead and trying this work. The exact mechanism of the cause of multiple sclerosis is not known and probably will not be known until sympathectomy is tried in a number of cases to see whether it is going to help or not. I think in a new field such as this that one should be careful to establish definitely the diagnosis of multiple sclerosis.

I should like to ask Dr. Wetherell whether lumbar punctures were done in his cases, and if so whether the spinal fluid was typical of that obtained in cases of multiple sclerosis.

Before Dr. Wetherell can be justified in drawing definite conclusions, I feel that a little longer time should elapse to be certain that the improvements noted are not the remissions that frequently occur in cases of multiple sclerosis. I think further that similar work should be tried. Possibly various modifications of this operation should be done, but I think that it is highly commendable, and every one will watch with great interest the progress in Dr. Wetherell's cases.

Dr. Henry W. Woltman, Rochester, Minn.: I think that most neurologists believe that multiple sclerosis is one of those diseases for which effective treatment will eventually be found, but so far the horizon has been scanned for many years in the hopes of finding something that would be truly helpful. I had not expected help from treatment of the nature of cervicodorsal sympathectomy and was rather astonished when the first article on this subject appeared.

There is one aspect of this method of treatment that I think is rather interesting. For a number of years multiple sclerosis has been treated with typhoid vaccine, with, I think, a certain degree of success. Injections of typhoid vaccine have also constituted a reliable test in cases of Raynaud's and of Buerger's disease in order to determine beforehand whether sympathectomy will be of benefit.

If injections of typhoid vaccine are of help in treating multiple sclerosis and if they result in temporary sympathectomy, there is a possibility that sympathectomy may help patients afflicted with multiple sclerosis. Any inferences on this basis regarding the etiology of multiple sclerosis, however, seem open to question.

Dr. Frederick S. Wetherell: My severest critics have been my own colleagues in Syracuse. I have had to stand against them ever since last November, when the first operation was performed. I know that this is a short time after which to make any statement as to end-results or as to the permanency of the effects of this operation. I am not proposing that it shall be accepted, but something must be done. The use of the operation must be continued until the first patient dies and an autopsy is performed. I already have permission to perform autopsy on the first two patients, so I shall discover perhaps just what has happened. Until that time, I am afraid one will have to wait, as far as the human being is concerned, to see the pathologic change that follows cervicodorsal sympathectomy.

I have no answer to Dr. Chambers' question as to the possibility of damage due to permanent vasodilatation. I cannot see why there should be any.

I was much interested in what Dr. Fay said. Dr. Retan, of Syracuse, "pushed" the use of forced spinal drainage clinically, and in New Orleans two years ago he reported on the results in many cases in which he had used this procedure. He also tried it in cases of multiple sclerosis. While he did get improvement for a short time, it was fleeting, and the patient was soon in his former condition.

Dr. Gardner spoke of the change in the spinal fluid pressure. A change, of course, undoubtedly occurs following sympathectomy. Perhaps my associates and I base our results somewhat on that.

Dr. Viets mentioned Dr. Tracy Putnam's work, and I cited it in this article and in a previous one. It follows closely Royle's work on the brain of the goat, which showed that congestion as revealed by the brain itself in the living goat was venous and was relieved following sympathectomy. There is a change in the venous circulation. Putnam was able to cause congestion by the injection of oil and, as Dr. Viets said, was able to produce a plaque which was similar to the plaque seen in cases of multiple sclerosis. I have not said that it was the same, but it looked the same.

Dr. Gardner asked about the histopathologic examination of the ganglia. We have examined all of them carefully with the hope that we might some day find some difference in them, and so far there has been evidence of inflammatory reaction in only one case. I believe that histopathologists will have to develop other methods of examination and perhaps other methods of staining and other ways of finding out what has happened in the sympathetic nervous system, just as Heinbecker in St. Louis has shown by various staining methods and with the oscillograph that there are definite pain fibers in the sympathetic nervous system.

Of course, it is my hope that my presentation will stimulate interest in the subject of multiple sclerosis and its treatment and that research workers who are much more able to do it than I will some day find the answers to the questions that have arisen concerning it.

I want to express my appreciation to Dr. Adson for the opportunity he gave me to learn the technic of cervicodorsal sympathectomy. The thing that made me feel more than anything else that we might be getting somewhere with this procedure was the fact that the other men who were treating this condition had been using typhoid vaccine and also an antigen. The vaccine produces a high fever reaction and a low chill reaction. Patients with multiple sclerosis treated by that method improve for a short time.

The effect of spinal drainage and of fever therapy, whether it is effected by vaccine or by some other means, is evanescent in nature. With cervicodorsal sympathectomy one causes vasodilatation which is permanent. There I shall leave the gauntlet.

EFFECT OF INTRACRANIAL TUMORS ON THE SELLA TURCICA

AN ANALYSIS OF FOUR HUNDRED AND FORTY-SIX CASES OF VERIFIED INTRACRANIAL TUMOR

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The diagnosis of intracranial tumors requires careful, precise and painstaking clinical investigation. In every case of suspected tumor of the brain the clinician is confronted by two distinct problems. The first is to ascertain the presence of a neoplasm, and the second is to localize such a lesion accurately. Until both problems have been solved rational surgical measures cannot be carried out. To attain this goal every available diagnostic procedure capable of lending aid must be employed. Of considerable value in many instances is a roentgen examination of the head.

Two methods are available in every roentgenologic study of the intracranial cavity. The first is the ordinary examination of the head, employing various projections and exposures. According to the second method, roentgenograms are made after the introduction of air into the intracranial cavity—either encephalography or ventriculography, depending on the method of injecting the air. While these methods are extremely valuable in selected cases, often revealing the precise location of a lesion of the brain, they are and must be regarded as formidable surgical procedures carrying with them a variable mortality. From the standpoint of the patient they are exceedingly trying and, to say the least, unpleasant ordeals. Furthermore, they can be employed only in hospitals and in institutions having a well organized neurosurgical service. For these reasons encephalography and ventriculography find limited application and should be reserved as a last resort after every other means of diagnosis has been exhausted. Ordinary roentgenograms of the head should be made to reveal as much information as possible, with the hope that such information will render injection of air unnecessary.

In the detection and localization of intracranial tumors by means of roentgen rays certain well established signs must be looked for, such as

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calcification of the tumor, alteration in the structure of the sella turcica, local erosions or hyperostoses of bone, displacements of the pineal gland and evidences of increased intracranial pressure manifested by convolutional atrophy of the inner table and thinning of the bones of the vault and widening of the sutures. Pancoast [1] in a recent contribution on the sella turcica said: "the sella is often the key to the tumor situation." Because of this fact the present study was undertaken to determine, first, the incidence of alterations in the sella turcica associated with intracranial tumors and, second, whether tumors in certain areas produce changes in the sella sufficiently characteristic to indicate the location of the lesion. For this purpose a careful study was made of the records

TABLE 1.—*Classification of Intracranial Tumors According to Location*

	Number of Cases	Number of Deformations	Percentage of Deformations
I. Supratentorial tumors	331	234	71
a. Cerebral tumors	216	130	60
1. Frontal lobe	61	36	59
2. Parietal lobe	55	25	45
3. Temporal lobe	78	57	73
4. Occipital lobe	15	9	60
5. Basal ganglia	7	3	43
b. Tumors of the midline	115	104	90
1. Pituitary	74	74	100
2. Suprasellar	22	19	86
3. Third ventricle	11	9	82
4. Pineal	5	2	40
5. Corpus callosum	3	0	0
II. Infratentorial tumors	115	54	47
a. Tumors of the cerebellar hemisphere	40	14	35
b. Tumors of the angle	37	23	62
c. Tumors of the midline	38	17	45
1. Cerebellar vermis	25	11	44
2. Fourth ventricle	8	4	50
3. Pons and medulla	5	2	40

and roentgenograms in 446 cases of verified intracranial tumor from the neurosurgical service of Dr. Charles H. Frazier, Hospital of the University of Pennsylvania.

The tumors were classified according to their location; table 1 indicates the number of lesions in each group. We recognize the difficulty of assigning tumors to specific localities since many are not confined to a single anatomic region but occupy two or even three of the designated areas. Furthermore, since our knowledge of the location of the tumor was derived chiefly from the operative notes and since we were cognizant of the difficulty experienced by the surgeon at times in appreciating the full extent of the lesion, we recognize that certain errors in the grouping of the cases must necessarily exist. Nevertheless, every possible

1. Pancoast, H. K.: The Interpretation of Roentgenograms of Pituitary Tumors, Am. J. Roentgenol. **27**:697 (May) 1932.

care was exercised in determining the true location of the tumor. When a lesion was found to occupy more than one region it was assigned to the portion of the brain most affected as determined from a careful study of all the data at hand. Autopsy records were consulted whenever available.

INCIDENCE OF SELLAR DEFORMATIONS

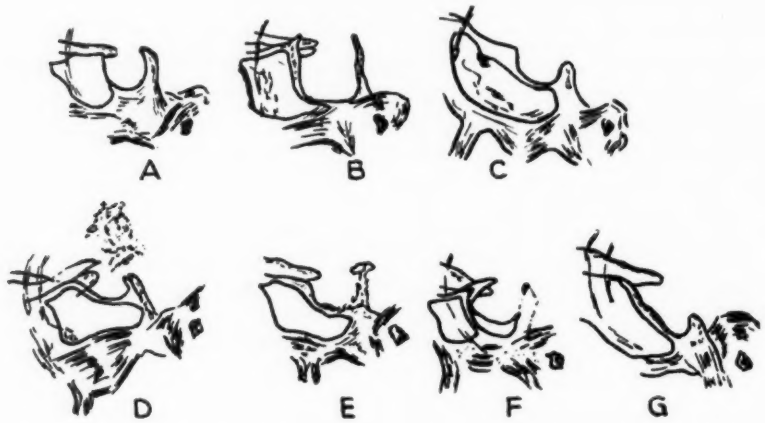
In this series of 446 cases there were 288 in which the roentgenograms showed deformity of the sella turcica—an incidence of 64.6 per cent. Thus it is seen that in approximately two thirds of all the cases of tumor of the brain one may expect some alteration in the structure of the sella turcica. In view of the fact that few conditions other than intracranial tumors produce deformity of the sella turcica such a finding is of considerable diagnostic value.

Of the 331 supratentorial lesions, 234, or 71 per cent, produced some change in the sella, while of 115 infratentorial tumors 54, or 47 per cent, caused sellar deformity. The cause for this variation will become apparent in the subsequent study of the individual groups. An analysis of the cases of supratentorial tumor confirms the well known fact that the degree of deformity of the sella turcica is in direct proportion to the proximity of the tumor to the sella. Thus it is seen that 90 per cent of the tumors of the midline produced sellar changes as compared to 60 per cent of the neoplasms occurring in the cerebral hemispheres which brought about such changes. Of the tumors of the midline, those occurring within the pituitary fossa gave rise to the highest percentage of deformations, namely 100 per cent. The type of deformity produced by intrasellar lesions is by far the most characteristic (fig. *B*). The marked enlargement and ballooned-out appearance of the pituitary fossa, encroachment on the sphenoid sinus, elongated and erect position of the dorsum sellae, retention of the posterior clinoid processes and pointed tuberculum sellae present an appearance which in many instances is pathognomonic of a pituitary adenoma. Of the 74 tumors of this type observed in this series 67, or 90.5 per cent, produced a deformity of the sella either characteristic or suggestive of an intrasellar lesion. In only 7 cases was the deformity atypical. It is thus seen that the great value ascribed to the roentgen examination in pituitary tumors is well founded.

The next highest percentage of deformities (86 per cent) occurred in the suprasellar group. Eleven of the 22 tumors produced an alteration regarded as characteristic of suprasellar tumors (fig. *C*), namely, moderate enlargement of the pituitary fossa, chiefly in the anteroposterior diameter, widening of the entrance to the pituitary fossa, absence of the posterior clinoid processes and a variable degree of erosion of the top of the dorsum sellae. In cases of these lesions, however, the

roentgen diagnosis is in many instances not so much dependent on the type of sellar deformity as on the presence of calcification in the tumor (fig. *D*). Eleven of the 22 suprasellar tumors were calcified. The type of neoplasm most commonly occurring just above the sella is the tumor of the hypophyseal stalk, of which there were 17 in the suprasellar group. Ten, or 59 per cent, of these showed calcification. McKenzie and Sosman [2] found that the incidence of calcification in a group of cases of similar tumors was 71 per cent. Thus the importance of calcification in the diagnosis of suprasellar tumors is apparent.

The tumors of the third ventricle, which are in reality suprasellar in position, were associated with deformity of the sella in 82 per cent of the cases studied. There was nothing characteristic, however, in the type of deformity found in these cases. Only two of the pineal tumors



Common types of sellar deformation found associated with intracranial tumors. *A*, the normal sella turcica; *B*, an intrasellar tumor; *C*, a suprasellar tumor; *D*, a suprasellar tumor with calcification; *E*, a tumor of the middle fossa; *F*, a parasellar tumor; *G*, a tumor of the posterior fossa.

and none of the tumors of the corpus callosum produced changes in the sella turcica; these figures again emphasize that the proximity of the lesion to the sella is the most important single factor in producing alteration in its appearance.

Of the tumors of the cerebral hemispheres, those occurring in or about the temporal lobe gave rise to the highest percentage of deformities, namely 73 per cent. Lesions in this locality often occupy a true parasellar position, that is, they are situated along the side of the pituitary fossa. In this position, direct pressure on the sella or pulsations

2. McKenzie, K. G., and Sosman, M. C.: The Roentgenological Diagnosis of Cranio-Pharyngeal Pouch Tumors, Am. J. Roentgenol. **11**:171 (Feb.) 1924.

transmitted from pressure on the internal carotid artery are responsible for the changes in the sella. The deformity associated with tumors of the temporal lobe is often characteristic (fig. *E*). The dorsum sellae shows slight but definite evidence of erosion; the posterior clinoid processes are intact, and the pituitary fossa is "top normal" or only slightly enlarged. When the tumor is parasellar in position there is often a definite unilateral erosion of the dorsum, with the appearance of a double floor to the fossa and involvement of but one anterior clinoid process (fig. *F*). Of the 57 deformities occurring in the group of tumors of the temporal lobe, 26 suggested a parasellar tumor, while 12 were indicative of a tumor in the middle cranial fossa. Of interest in this connection are the so-called tumors of the sphenoid ridge, of which there were 7 in this series. Six produced definite deformity of the sella turcica. In 5 instances the deformity was of the type produced by a parasellar tumor, and in 1 it suggested a suprasellar tumor.

The lesions of the frontal and occipital lobe produced about the same percentage of deformities, namely, 59 and 60, respectively. Alteration of the sella turcica by tumors of the brain has long been attributed to one of two causes: either the direct pressure of the lesion on the sella or, through the medium of an internal hydrocephalus, the downward pressure of a dilated third ventricle on the sella, producing marked erosion of the bone. In recent years we have been somewhat impressed by the frequency with which tumors of the frontal lobe are associated with changes in the sella turcica. As this survey indicates, about three fifths of such lesions are associated with sellar deformity. As many of these tumors are unaccompanied by internal hydrocephalus, one cannot account for the deformity on this basis. Space-taking tumors produce a generalized increase in intracranial pressure, the amount depending on the size of the growth. The central location and the exposed position of the sella at the base of the skull predispose it to the effects of increases in intracranial pressure. Such pressure is, no doubt, an important factor in many of the sellar deformities occurring in cases of tumor unassociated with either internal hydrocephalus or direct pressure on the sella. Tumors growing in the frontal lobe often attain considerable size before producing clinical manifestations. They are among the largest tumors found in the intracranial cavity, and considerable increase in intracranial pressure is thus often produced. Many of these tumors invade the middle cranial fossa, and this no doubt accounts for the fact that of the 36 deformities occurring in the frontal lobe 7 were indicative of a parasellar tumor, and 10 were indicative of a lesion of the middle fossa. A tumor of the frontal lobe may at times grow backward over the sella turcica; thus, in 2 instances the deformity was of the suprasellar variety. The tumors of the frontal lobe as a group, however, produced no characteristic deformity of the sella turcica.

The manner in which tumors of the occipital lobe produce sellar changes is much the same as the process explained for lesions of the frontal lobe. The neoplasm may become of considerable size before it is detected and may produce a considerable increase in intracranial pressure. Probably of equal importance in this connection is the intimate association of some of these tumors with the tentorium cerebelli. As will become apparent from our consideration of tumors of the cerebellopontile angle, there is reason to believe that traction and distortion of the tentorium have much to do with altering the contour of the sella turcica. The anterior edge of each lateral portion of the tentorium passes forward to find attachment to the dorsum sellae by way of the petroclinoid ligaments. Through the dorsum sellae the tentorium has an indirect attachment to the diaphragma sellae. It is thus readily appreciated that disturbances in tension and distortion of the tentorium can readily affect the bony structure of the sella. With such variable factors as increase in intracranial pressure and indirect effects by way of dural attachments a characteristic type of deformity of the sella was not to be anticipated in cases of tumors of the occipital lobe. The location of these lesions could not be determined from the appearance of the deformed sella.

We had the preconceived idea that the tumors of the parietal lobe would be associated with a larger percentage of deformities than either frontal or occipital lesions, but this proved not to be the case. Only 45 per cent of these tumors affected the sella turcica. The reason for this, no doubt, is to be found in the fact that lesions of the parietal lobe frequently give rise to early and well defined symptoms as the result of involvement of the sensory area and close proximity to the motor area of the brain. The lesions are, therefore, as a rule smaller than those in the frontal and occipital lobes. Also in cases of tumors of the parietal lobe there is usually no cause for internal hydrocephalus, and only a minimum effect is to be expected from tension and distortion of the dura. It is interesting to note that three fifths of the 25 deformities encountered in this group indicated a lateral location of the lesion in respect to the sella turcica. The deformity in 6 cases was of the parasellar variety, and in 9 it was that found associated with tumors of the middle fossa.

We were interested in ascertaining the effect produced on the sella by tumors arising from the falx cerebri. Fourteen such tumors, all meningeal fibroblastomas, were observed in this series; 8 were in the frontal, 5 in the parietal, and 1 in the occipital, region. Eight of the 14, or 57 per cent, produced sellar deformities; 7 of the 8 growths were in the frontal lobe.

The percentage of deformities found associated with tumors of the basal ganglia was somewhat disappointing. Of the 7 tumors in this group, only 3, or 43 per cent, affected the sella. The close proximity of these lesions to the sella led one to expect a higher percentage of deformities. When one considers, however, that these tumors do not, as a rule, produce much increase in intracranial pressure, do not cause much distortion of the brain and seldom produce internal hydrocephalus, the lack of changes in the sella turcica is more readily understood.

Next to the intrasellar and suprasellar tumors, those occurring in the posterior cranial fossa or infratentorially are the ones most readily recognized roentgenologically. This recognition, however, is dependent not on the changes found in the sella turcica but rather on the roentgen manifestations of increased intracranial pressure. Deformities were encountered in only 47 per cent of the infratentorial group as compared with 71 per cent in the supratentorial group. With the exception of the group for tumors of the cerebellopontile angle, in none of the various groups of infratentorial tumors did the number of deformities exceed 50 per cent. On the basis of an internal hydrocephalus one might have anticipated a higher percentage of sellar deformations because tumors in the posterior fossa, especially those occurring in the midline, are prone to encroach on and occlude the fourth ventricle and the aqueduct of Sylvius. Yet as a group the tumors of the midline produced deformities in only 45 per cent of the cases. In respect to this paradoxical situation one finds that age is the all-important factor. In the cases of infratentorial tumors it was found that 44 per cent of the patients were 20 years of age or less, while in the cases of supratentorial tumors only 17 per cent of the patients were in that age group. It is in this group of patients that one finds the typical roentgen manifestations of increased intracranial pressure, such as an increase in the size of the head, a widening of the sutures, a convolutional atrophy and thinning of the bones of the vault. In the presence of an increasing intracranial pressure, erosion and enlargement of the sella turcica are prevented by the occurrence of the changes mentioned, especially widening of the sutures, which at this age are still ununited. Furthermore, in infants and young children the sella turcica is small, and the various structures are thick and stockily built and less prone to show the effects of pressure. The influence of age is well illustrated in the cases of infratentorial tumors of the midline, in only 45 per cent of which was a sellar deformity found. These lesions almost invariably produce internal hydrocephalus, sometimes of enormous size, with marked increase in intracranial pressure. In this group 71 per cent of the patients were less than 20 years of age. On the other hand, tumors of the third ventricle also occur in young persons, 73 per cent of the patients with

such tumors being 20 years of age or less. Yet in this group 82 per cent of the tumors had deformed the sella, the suprasellar position of these lesions superseding the effect of age.

Of unusual interest are the tumors of the cerebellopontile angle. We have generally regarded them as capable of producing but little effect on the sella turcica, yet in this analysis deformities were found in 62 per cent of the cases. These tumors differ decidedly from other infratentorial lesions. They are encountered in older persons, only 11 per cent occurring in patients below 20 years of age, as contrasted with 44 per cent, the figure for the combined types of infratentorial tumors occurring in the same age group. Age is therefore one factor responsible for sellar deformities in tumors of the angle. Another factor of considerable importance is the intimate relationship of these lesions to the tentorium and the effect produced on the sella by involvement of that structure. Tumors of the angle also show a marked tendency to distort the brain. Fourteen of the 23 deformities occurring in this group were suggestive of either a parasellar lesion or a tumor of the middle fossa. This effect, no doubt, is produced in many instances by traction on one side of the sella through the medium of the tentorium and petroclinoid ligaments. In addition, some of these tumors show a definite tendency to invade the middle cranial fossa.

Tumors occurring in the posterior fossa have generally been regarded as producing a fairly characteristic type of sellar deformity (fig. *G*). This consists of erosion of the top of the dorsum sellae with frequently complete absence of this structure. The pituitary fossa, especially the posterior portion, often shows marked enlargement with encroachment on the sphenoid sinus. This deformity is usually attributed to direct pressure from a dilated third ventricle. The frequency of this type of deformity in the cases of infratentorial tumors in this series fell short of our expectations, only 9 of the 54 deformities being of this character. On the other hand, 22, or slightly less than half, of the deformities suggested a lesion of the middle cranial fossa. It is thus seen that in the roentgen diagnosis of infratentorial tumors one cannot rely on the type of sellar deformity found associated with these lesions.

TYPE OF SELLAR DEFORMATIONS

As previously stated, one of the purposes of this study was to determine whether the type of sellar deformation is of any value in the localization of intracranial tumors. The approach to this phase of the subject was the interpretation of the appearance of the sella turcica in 674 roentgenograms of the head. These roentgenograms included films made in the 446 cases forming the basis of this report, in many cases of undoubted tumor of the brain which were not verified and in

a large number of cases in which the patients were examined for a variety of conditions unassociated with intracranial neoplasms. Thus the interpretations were made without knowledge of whether the patient had a tumor of the brain or of the location of such a lesion. Every effort was made not to be influenced by other manifestations of tumor which might be present in the roentgenograms. Of the 288 sellar deformities occurring in this series, the type of deformation was sufficiently characteristic in 141, or 49 per cent, to suggest the approximate position of the tumor exclusive of its lateralization. To determine the side on which a tumor is located one must usually depend on the clinical data, although not infrequently other roentgen manifestations serve to lateralize the lesion. The accuracy of localization from the type of sellar deformity was greatest in the cases of pituitary lesions and of those of the suprasellar, temporal and parietal lobe. In other regions of the intracranial cavity the type of sellar deformity was of little aid in localizing the tumor.

HISTOLOGIC DATA

In an attempt to determine the factors responsible for the deformation of the sella turcica by intracranial tumors, the histologic nature of the lesions and certain clinical data were analyzed. Histologically, in number and order of frequency the lesions were classified as follows: gliomas, 180; meningeal fibroblastomas, 69; pituitary adenomas, 63; tumors of the hypophyseal stalk, 19; perineural fibroblastomas, 12; metastatic tumors, 8, and sarcomas, 8. There was a variety of other lesions, but the number in each group was too small to determine their effect on the sella turcica. Sellar deformity occurred most frequently in the cases of pituitary adenomas. In only 1 instance, that of a suprasellar adenoma, was there no alteration. Seventeen of the 19 tumors of the hypophyseal stalk affected the sella. Two lesions in that group were intrasellar. Of particular interest is the effect produced by the meningeal fibroblastomas and the gliomas. In the fibroblastoma group the sella was deformed in 71 per cent of cases, while in the glioma group deformations occurred in only 48 per cent of instances. This was an unexpected result. As a rule the fibroblastomas grow much more slowly, less seldom produce internal hydrocephalus or marked increase in intracranial pressure and do not attain the large size so often shown by the gliomas. The cause for the difference in the effect on the sella of these two types of lesions is not entirely clear. In the region of the temporal lobe, where 15 of the 18 fibroblastomas produced sellar changes, the effect is obviously due to the proximity of the lesion to the sella. The tumors in this region are firm and unyielding, in consequence of which they are capable of

producing considerable erosion by direct or transmitted pressure. Proximity, however, cannot account for the results observed in cases of fibroblastomas occurring in other regions; for instance, deformation of the sella was produced by 12 of the 19 tumors in the frontal region, 8 of the 14 in the parietal region and all of the 4 in the occipital region. Of the 14 fibroblastomas arising from the falx, 8 deformed the sella. The explanation which suggests itself for this tendency of the fibroblastomas to alter the sella is that while most of these tumors have their origin from the arachnoid, their relation to the dura is intimate. The tension and distortion produced by these tumors are transmitted to the sella by way of the dura. The influence of the dura, falx and tentorium on the structure of the sella turcica has become increasingly apparent throughout this study. Alpers [3] has suggested another possibility which must be considered as regards the sellar effects of the fibroblastomas, namely, that these lesions may indirectly obstruct the circulation about the sella. Circulatory stasis, dilatation of the vascular channels and excessive accumulations of cerebrospinal fluid in the basal cisterns about the sella are potent factors in producing sellar alterations.

In considering the gliomas as a group we were somewhat surprised to observe that the astrocytomas, the most slowly growing tumors of this type, produced the greatest number of deformations in the sella, 51 per cent. In contrast the multiform spongioblastomas, the largest and most rapidly growing gliomas, deformed the sella in only 35 per cent of instances. This suggests that the rapidity of growth of a tumor is another factor of considerable importance in determining whether the sella turcica will be deformed. This is in keeping with the high percentage of deformations found in the cases of the slowly growing fibroblastomas. There were only 3 oligodendrogliomas, all of which deformed the sella. Of the medulloblastomas, only 11 per cent produced sellar changes. Although these tumors are often large and are frequently associated with marked internal hydrocephalus, the cause for the low percentage of sellar deformities becomes apparent when one considers the age incidence of this tumor. Two thirds of the medulloblastomas occurred in patients less than 20 years of age. There were 12 perineural fibroblastomas, 6 of which produced sellar deformities. Slow growth and involvement of the dura appear to account for this effect. Of the 8 metastatic neoplasms, 5 produced sellar deformities, and of the 8 primary sarcomas, 3 were associated with alteration of the sella. As regards deformation of the sella turcica, it seems that the histologic type of the tumor is considerably less important than its position, its rate of growth, the involvement of the dura and the age of the patient.

3. Alpers, B. J.: Personal communication to the authors.

CLINICAL DATA

An attempt was made to correlate certain clinical data with the occurrence of deformation of the sella turcica. The duration of symptoms is not, of course, a precise indication as to the duration of the lesion. There was a tendency toward a greater number of deformities in the cases with symptoms of long duration, again indicating that the rate of growth of the lesion is of some importance. As regards the increase in spinal fluid pressure and the occurrence of choked disk and optic atrophy, there was a definite tendency to sellar deformity in the group of patients presenting these manifestations. As the mechanism producing these changes is also responsible for sellar deformations, this correlation was more or less to be expected. There were many exceptions, however. In the cases of infratentorial tumors, in which increased spinal fluid pressure and choked disk were common, sellar deformities were relatively uncommon. Here again the influence of age was operative. On the other hand, in cases of intrasellar lesions, in 100 per cent of which deformity of the sella occurred, increased intracranial pressure and choked disk were exceedingly uncommon. As regards the size of the tumor, it was impossible to determine the exact dimensions of the lesions except at postmortem examination. There was no certain correlation between the size of the tumor and the occurrence of sellar deformity. This factor was offset by other considerations, such as the position of the lesion, the rapidity of growth and the age of the patient. The largest tumors occurred in the frontal region; they were associated with deformations in only 59 per cent of instances, while the smallest lesions, occurring in the midline, showed the largest percentage of deformities. As regards the clinical manifestations considered, there were so many exceptions and so many variable factors that, on the whole, no reliable correlation with the occurrence of sellar deformation could be determined.

OTHER ROENTGEN MANIFESTATIONS OF INTRACRANIAL TUMOR

Since deformation of the sella turcica is only one of the roentgen manifestations of intracranial tumors, it is interesting to note the frequency of its occurrence as compared with other changes. In 78 per cent of the cases in this series there was some roentgen evidence of an intracranial tumor. In 47 per cent of the cases the only manifestation was an alteration in the sella turcica, while in 13 per cent some abnormality other than sellar deformity was present. In 18 per cent sellar deformation was combined with some other change. In 65 per cent of the cases in the series there was deformation of the sella turcica, as compared with 31 per cent in which there were other roentgen manifestations. It is thus seen that as a diagnostic sign of

intracranial tumor deformation of the sella turcica occurs approximately twice as frequently as all other signs combined. As regards other recognized roentgenologic changes indicative of tumor of the brain, the incidence of these together with deformation of the sella occurring in this series is given in table 2.

Some pertinent facts relative to other roentgen manifestations of tumor of the brain became apparent from this study. Of the 29 calcified lesions, 38 per cent were suprasellar in position. A lateral shift of a calcified pineal gland occurred only in cases of lesions of the temporal and parietal lobes. Of the 13 tumors producing localized erosion of the bone 69 per cent were tumors of the angle. There were 8 cases of localized hyperostosis of bone, 6 occurring in patients with fibroblastomas. Of the lesions showing convolutional atrophy, 63 per cent were infratentorial tumors, while 81 per cent of the tumors associated with widening of the sutures were also situated below the

TABLE 2.—*Incidence of the Various Roentgen Manifestations of Intracranial Tumors Occurring in This Series*

Nature of Manifestation	Percentage
Deformation of the sella turcica	64.6
Convolutional atrophy	8.8
Calcification of the tumor	6.5
Widening of the sutures	4.6
Local erosion of the bone	2.9
Local hyperostosis	1.8
Lateral shift of the pineal gland	1.8
Widening of the diploic channels	0.2

tentorium, indicating that these changes have a definitely higher incidence in children and young adults.

SUMMARY AND CONCLUSIONS

In this series of 446 cases of verified intracranial tumor, alterations in the structure of the sella occurred in 64.6 per cent, indicating that as a roentgen manifestation of tumor of the brain sellar deformations may be expected to occur in approximately two thirds of all the cases. Its frequency is about twice that of all other roentgen manifestations of tumor of the brain combined. It appears from this study that the factors which influence the occurrence of deformation of the sella are as follows: (1) proximity of the lesion to the sella, (2) age of the patient, (3) direct pressure from a dilated third ventricle accompanying an internal hydrocephalus, (4) increase in intracranial pressure, (5) rate of growth of the tumor, (6) involvement of the dura by the tumor and (7) circulatory stasis and accumulations of cerebrospinal fluid about the sella. The most important single factor is the proximity of the tumor to the sella, as indicated by the fact that 90 per cent of

the midline supratentorial tumors deformed the sella, as compared with 60 per cent of the cerebral lesions. The influence of the age of the patient is evidenced in the difference between the incidence of deformities in cases of supratentorial tumors, 71 per cent, and that in cases of infratentorial tumors, 47 per cent. Of the lesions in the latter group 44 per cent occurred in patients 20 years of age or less, while only 17 per cent of the patients with supratentorial lesions were in the same age group. This influence of age is due to the fact that before the closure of the cranial sutures takes place various means are available to compensate for increases in intracranial pressure, which prevent the effects of abnormal pressure on the sella turcica. Direct pressure from a dilated third ventricle is observed in many cases of lesions obstructing the aqueduct of Sylvius or the fourth ventricle. In the cases of tumors of the frontal lobe were found the best examples of sellar deformation due to an increase in intracranial pressure. As regards the effect of the rate of growth of the tumor, the largest number of deformities occurred in the cases of more slowly growing lesions, as indicated by the relatively high percentages obtained for the fibroblastomas and astrocytomas. The importance of the involvement of the dura by the tumor is indicated by the relatively high percentage of alterations occurring with tumors of the occipital lobe and of the cerebellopontile angle and with the fibroblastomas.

Histologically, deformities of the sella occurred most frequently in association with the pituitary adenomas, tumors of the hypophyseal stalk, fibroblastomas and astrocytomas, in the order given.

Some of the more important clinical manifestations of tumor of the brain were analyzed in an endeavor to determine any correlation which might exist between them and the occurrence of sellar deformations. The sella appeared to be affected more frequently in patients with symptoms of long duration; sellar deformities were commonly associated with increases in spinal fluid pressure and with choked disk and optic atrophy. There were many exceptions, however, so that no truly reliable correlation could be established.

One of the prime purposes of this study was to determine whether recognition of the type of sellar deformity was helpful in indicating the location of the tumor. In approximately one half of the cases in which the sella was affected the type of deformity was sufficiently characteristic to suggest the location of the tumor exclusive of its lateralization. Accuracy of localization was greatest in the cases of pituitary and suprasellar tumors and of growths in the temporal and parietal lobes. The type of sellar deformity was of little value in the localization of tumors in other parts of the intracranial cavity.

RELATION OF HYPOTHALAMICO-HYPOPHYSEAL SYSTEM TO DIABETES INSIPIDUS

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The present report is primarily concerned with the polyuria or experimental diabetes insipidus, observed during an investigation of the effects of lesions in the hypothalamus of the cat, and with the attempt to localize the precise nuclear groups within this region which are involved in the regulation of water exchange. The mammalian hypothalamus has been held to be the chief regulating center for a large number of vegetative processes, such as water, fat and carbohydrate metabolism, the regulation of temperature, pupillary dilatation, the regulation of blood pressure and so on, but, aside from the work of Ranson and Magoun [1] and of Kabat, Magoun and Ranson,[2] who obtained marked respiratory acceleration, rises in blood pressure and pupillary dilatation by stimulation of the lateral hypothalamic area and the region around the fornix, and the work of Broers,[3] who showed that destruction of the supra-optic nuclei results in diabetes insipidus, the problem of hypothalamic localization is practically unsolved.

During the course of this investigation it has been found impossible to proceed far without taking into consideration the functional and anatomic relations which exist between the hypothalamus and the pituitary gland. It should be noted that many of the functions attributed to the hypothalamus have from time to time been held to belong to the hypophysis. In recent years, especially since it has become generally recognized that there are neural and vascular connections between the two regions, it has become common to speak of the diencephalic-hypophyseal mechanism and to consider the two structures as a functional, reciprocally interacting unit. Nevertheless, the manner in which the mechanism works is still obscure. It is now well established that a heavy bundle of unmyelinated fibers connects the hypothalamus with

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1. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933.

2. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of the Hypothalamus, Proc. Soc. Exper. Biol. & Med. **31**:541, 1934.

3. Broers, H.: Experimenteele Diabetes Insipidus, Thesis, Utrecht, 1932.

the posterior lobe of the pituitary by way of the pituitary stalk, but the precise origin and termination of the bundle are still in dispute, and whether it conveys secretory, inhibitory or sensory impulses is not settled. The diencephalic-hypophyseal system has been held to function in the regulation of water metabolism, but as late as 1932 Cushing [4] pointed out that it is not known whether diabetes insipidus is caused by irritative or by destructive processes.

According to many investigators, not only is there a play of nervous impulses from the hypothalamus on the pituitary gland, but the hypophyseal secretions in their turn activate and tone the tuberian centers. Cushing has long been an advocate of the theory that the secretions of the pars intermedia activate the hypothalamus,[5] and Collin [6] has described several routes by which the hypophyseal colloidal secretion may reach the hypothalamus, namely, by way of the general circulation, through the cerebrospinal fluid of the third ventricle by way of the pituitary stalk, by direct secretion into the tuber cinereum or by way of the hypophyseoportal system of Popa and Fielding.[7]

Because of the minuteness of the region in question and because of the anatomic adjacence of the hypothalamus and the pituitary gland, it has been almost impossible to stimulate or make lesions in one or in the other without involving both. As a consequence, the attempts at hypothalamic localization have led to conflicting results. Moreover, in the few millimeters between the optic chiasma and the mamillary bodies there are more than a dozen different nuclei, and with the ordinary methods one is unable to isolate and attack one alone. Referring to diabetes insipidus, Cushing [4] has remarked that "not until it will be possible to evolve some method of first stimulating and then of destroying the definite cluster of nerve-cells (presumably the nucleus supraopticus) which governs the response can we begin to feel that we have touched bottom in this watery topic."

A method which to some extent fulfils the conditions set forth by Cushing and with which lesions can be localized with a great degree of accuracy exists in the Horsley-Clarke stereotaxic instrument. The technic employed with this instrument in the laboratory with which we are associated has been described by Ranson.[8] With this apparatus it

4. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

5. Cushing, H.: (*a*) Posterior Pituitary Activity from an Anatomical Standpoint, Am. J. Path. **9**:539, 1933; (*b*) footnote 4.

6. Collin, R.: Existe-t-il des preuves expérimentales de la neurocrine hypophysaire? Ann. de méd. **33**:239, 1933.

7. Popa, G., and Fielding, U.: A Portal Circulation from the Pituitary to the Hypothalamic Region, J. Anat. **65**:88, 1930.

8. Ranson, S. W.: On the Use of the Horsley-Clarke Stereotaxic Instrument, Psychiat. en neurol. bl. **38**:270 (May-Aug.) 1934.

is possible to approach the hypothalamus from above without disturbing the hypophysis, as usually happens in operations performed by the buccal route, and without putting tension on the infundibulum, as happens in operations performed by the temporal approach.

SURVEY OF THE LITERATURE ON DIABETES INSIPIDUS

The experimental and clinical literature on diabetes insipidus is extensive, and space does not permit of a complete presentation. Within the last few years several excellent reviews of the subject have appeared. Roussy and Mosinger [9] summarized in detail the present position of the French school, which under the direction of Camus first demonstrated that diabetes insipidus could be elicited by hypothalamic puncture. Leschke [10] reviewed the clinical and experimental evidence in favor of the hypothalamic origin of diabetes insipidus. Perhaps the best and most complete survey is that of Staemmler,[11] in which more than three hundred titles were included. In this article ample evidence is presented to show that isolated lesions either of the hypothalamus or of the posterior and intermediate lobes of the hypophysis may result in diabetes insipidus.

At this time we wish to present briefly the results of several recent investigations which have not been treated in the summarizing articles already mentioned. Richter [12] produced permanent polyuria in three rats in which the pituitary stalk was separated and the anterior and posterior lobes of the hypophysis were left intact. Somewhat similar results were reported by Cushing.[4] Under the latter's direction Maddock placed silver clips at various levels on the hypophyseal stalk in a series of dogs. In one of the animals marked polyuria, with an average daily output of 5 liters, developed and persisted for nearly two years. It was found that the nerve fibers in the stalk distal to the point of application of the clip were absent. Compère [13] and Brull [14] provided evidence that the polyuria following hypophysectomy is of hormonal origin. They were able to show that the polyuria and

9. Roussy, G., and Mosinger, M.: Le tuber cinereum et son rôle dans les principales fonctions du métabolisme: métabolisme de l'eau, des glucides et des lipides, Ann. de méd. **33**:193, 1933.

10. Leschke, E.: Diabète insipide et système hypothalamo-hypophysaire, Ann. de méd. **33**:261, 1933.

11. Staemmler, M.: Diabetes insipidus und Hypophyse, Ergebn. d. allg. Path. u. path. Anat. **26**:59, 1932.

12. Richter, C. P.: Cyclical Phenomena Induced in Rats by Section of the Pituitary Stalk and Their Possible Relation to Pseudopregnancy, Am. J. Physiol. **106**:80, 1933.

13. Compère, A.: Mécanisme de la polyurie hypophysaire, Arch. internat. de physiol. **36**:54, 1933.

14. Brull, L.: Transmission sanguine de la polyurie hypophysaire, Presse méd. **41**:1267, 1933.

hypochloruria accompanying hypophysectomy are transmissible through the blood stream to the kidneys of a normal dog by way of the carotid-jugular circulation.

The most recent work on the relation of the hypothalamus to diabetes insipidus has been done in Holland by Broers.[15] In this careful investigation permanent polyuria was produced in three dogs, in one after bilateral destruction of the supra-optic nucleus, in the second after destruction of the floor of the pituitary stalk and in the third after complete hypophysectomy and damage to the medial part of the hypothalamus. In all of these animals there was atrophy of the supra-optic and the paraventricular (filiform) nuclei. In the dog with bilateral destruction of the supra-optic nucleus Broers noted marked atrophy of the posterior lobe; in another animal with unilateral destruction of the supra-optic nucleus he observed homolateral atrophy of the posterior lobe. It was concluded that the supra-optico-hypophyseal system is a regulating mechanism for salt metabolism and that diabetes insipidus is due to a disturbance of this system.

Most of the recent investigators, Roussy and Mosinger,[9] Leschke,[10] Cushing,[4] Staemmler[11] and others, have attempted to reconcile the theory of a hypophyseal origin of diabetes insipidus with that of a hypothalamic origin by postulating a reciprocal interaction between certain of the hypothalamic nuclei and the pituitary gland. In view of the now well established fact that the hypothalamus and the hypophysis have neural and vascular connections (Roussy and Mosinger[16] and Popa and Fielding[7]), these workers conceived of nervous impulses from the tuberian region as acting on the pituitary gland and of the secretions of the latter as passing through the infundibulum into the third ventricle and acting on the hypothalamic centers by the different routes outlined by Cushing[5a] and by Collin.[6] Cushing[4] summarized the possible relationship of the diencephalic-hypophyseal system and diabetes insipidus in the following words:

> So far, then, as diabetes insipidus is concerned, the evidence at hand seems reasonably convincing that the disorder can be produced by nuclear degeneration from disease, by surgical injuries of the supraoptic region in operations about the chiasm, by the interruption of the nerve tracts in course whether from tuberal tumors, or punctures, by the experimental placement of a compressing clip on the infundibulum and probably also (could this be accomplished) by complete removal of the epithelial investment which apparently elaborates the posterior lobe secretion—all of which indicates a diencephalo-hypophyseal mechanism which can be broken at any of three principal points—nucleus, fiber tract, and pars intermedia

15. Broers, H.: Experimentelle Diabetes insipidus, Arch. di sc. biol. **18**:83, 1933. Winkler, C.: Manuel de neurologie, Haarlem, de Erven F. Bohn, 1933, vol. 1, pt. 5. Broers.[3]

16. Roussy, G., and Mosinger, M.: Rapports anatomiques et physiologiques de l'hypothalamus et de l'hypophyse, Ann. de méd. **33**:301, 1933.

et tuberalis. We nevertheless, in regard to this most carefully studied of all diencephalo-hypophyseal reactions, are left in some doubt as to whether the phenomenon is stimulatory or paralytic.

METHODS

During the course of the present investigation lesions have been produced in various parts of the hypothalamus in more than sixty adult cats. For this purpose the Horsley-Clarke stereotaxic instrument was employed in a manner similar to that utilized by Ingram and Ranson [17] in placing lesions in the red nuclei in cats.

After operation the animals were placed in metabolism cages. The urine of each animal was collected and measured and the specific gravity determined each morning. At the same time a measured amount of water was given, and at the end of the twenty-four hour period the amount of water remaining was measured and allowance made for evaporation. The amount of water given was always more than sufficient for the animal's needs. The diet was carefully regulated. One group of cats was fed 100 Gm. of ground beef heart and 100 cc. of milk daily, while a second and larger group was placed on a diet of 60 Gm. of beef heart and 100 cc. of milk (table 5), which was found just sufficient to maintain the weight of a normal, average-sized cat at a fairly constant level. The food was given in the morning, and the amount left over, if any, was collected and the quantity noted in the afternoon. A group of twenty-five normal animals was treated in the same manner (table 3). Many of the normal cats were subsequently operated on (tables 3, 4 and 5), so the effects of the operation on water exchange were adequately controlled. In these cases the constancy of the diet for the periods before and after operation makes the figures for the output of urine and those for the intake of fluid comparable.

At the end of the period of observation the animals were killed by bleeding, and a dilute solution of formaldehyde U. S. P. (1 : 10) was injected into the head. The brain was removed and embedded in pyroxylin. The hypothalamus with the hypophysis attached was cut serially, and the sections were stained with cresyl violet for cells and by Weil's method for myelinated fibers.

RESULTS

Anatomic Considerations.—In the description of the lesions the terminology used by Ingram, Hannett and Ranson [18] and by Rioch [19] has been adopted. We are particularly interested here in two nuclei, the supra-optic or tangential nucleus and the filiform or paraventricular nucleus. Confusion will be avoided if the reader carefully notes at this point that the paraventricular nucleus is the same as the filiform and that the tangential nucleus is the same as the supra-optic. The latter nucleus forms a sort of a cap over the optic tract about 3 mm. lateral to the third ventricle. The principal portion of the nucleus lies dorsal

17. Ingram, W. R., and Ranson, S. W.: Effects of Lesions in the Red Nuclei in Cats, Arch. Neurol. & Psychiat. **28**:483 (Sept.) 1932.

18. Ingram, W. R.; Hannett, F. I., and Ranson, S. W.: The Topography of the Diencephalon of the Cat, J. Comp. Neurol. **55**:333, 1932.

19. Rioch, D. M.: Studies on the Diencephalon of Carnivora: I. The Nuclear Configuration of the Thalamus, Epithalamus, and Hypothalamus of the Dog and Cat, J. Comp. Neurol. **49**:1, 1929.

to the tract and extends a short distance rostrally, while a second, smaller portion lies on the caudal surface of the tract. Frequently, an accessory supra-optic nucleus is seen medial to the principal rostral mass, sometimes forming a bridge between the principal portion and the filiform nucleus. The filiform nucleus is divided into an anterior part, which lies in the rostrodorsal part of the hypothalamus near the ventricle, and a principal part caudal to the anterior portion and just ventral to the floor of the thalamus. These two nuclei, especially the supra-optic, have been described as sending a heavy bundle of unmyelinated fibers down the pituitary stalk to the posterior lobe (Kary,[20] Lewy,[21] Pines,[22] Greving,[23] Stengel,[24] Espino Vergara,[25] Croll,[26] Nicolesco and Nicolesco,[27] Maiman,[28] Mogilnitsky,[29] Cushing,[4] Collin,[6] Bucy [30] and Roussy and Mosinger [16]).

Roussy and Mosinger [16] have given the most detailed description of the neural connections between the hypothalamus and the hypophysis, and our own observations most nearly correspond to theirs. The axons from the cells of each supra-optic nucleus loop over the optic tract,

20. Kary, C.: Pathologisch-anatomische und experimentelle Untersuchungen zur Frage des Diabetes insipidus, Virchows Arch. f. path. Anat. **252**:734, 1924.

21. Lewy, F. H.: Infundibuläre Veränderungen bei Diabetes insipidus und die Beziehungen zwischen Tuber cinereum und Hypophyse, abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **37**:397, 1924.

22. Pines, I. L.: Ueber die Innervation der Hypophysis cerebri: II. Ueber die Innervation des Mittel- und Hinterlappens der Hypophyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:123, 1926.

23. Greving, R.: (*a*) Beitrag zur Innervation der Hypophyse, Klin. Wchnschr. **4**:2181, 1925; (*b*) Beiträge zur Anatomie der Hypophyse und ihrer Funktion: I. Eine Faserverbindung zwischen Hypophyse und Zwischenhirnbasis (Tr. supraoptico-hypophyseus), Deutsches Ztschr. f. Nervenh. **89**:179, 1926; (*c*) Das Zentralnervensystem, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 4, pt. 1; (*d*) Das Zwischenhirn-Hypophysensystem: Seine Morphologie, Phylogenese und klinische Bedeutung, Klin. Wchnschr. **7**:734, 1928.

24. Stengel, E.: Ueber den Ursprung der Nervenfasern der Neurohypophyse im Zwischenhirn, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **28**:25, 1926.

25. Espino Vergara, A.: Contribucion al estudio de las relaciones entre la hipofisis y los centros diencephalicos, Thesis, University of Mexico, 1924.

26. Croll, M. M.: Nerve Fibers in the Pituitary of a Rabbit, J. Physiol. **66**: 317, 1928.

27. Nicolesco, I., and Nicolesco, M.: Quelques données sur les centres végétatifs de la région infundibulotubérienne et de la frontière diéncéphalo-télencéphalique, Rev. neurol. **2**:289, 1929.

28. Maiman, R.: Ueber die Zentren der Hypophysis cerebri, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:666, 1930.

29. Mogilnitsky, B. N.: Zur Frage über den Zusammenhang der Hypophyse mit dem Zwischenhirn, Virchows Arch. f. path. Anat. **267**:263, 1928.

30. Bucy, P. C.: The Hypophysis Cerebri, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 765.

course for a short distance along the base of the tuber and pass down the ventral wall of the stalk (fig. 29). We wish to stress the superficial course of this bundle along the base of the tuber. Probably some of the cells of other nuclei rostral to the stalk, namely, the anterior hypothalamic nucleus, the ventral periventricular hypothalamic nucleus and the ventromedial hypothalamic nucleus, likewise send their axons down the ventral wall of the stalk. The fact that fibers from the hypothalamus pass down the dorsal wall of the stalk has been stressed only by Roussy and Mosinger.[16] This bundle appears to be made up of finer axons than is the ventral tract and to be somewhat smaller. Because of the dense meshwork of fibers in the hypothalamus the precise origin of the fibers of the dorsal bundle is difficult to determine. Fibers appear to pass into it from a considerable area of the posterior part of the hypothalamus and from the region immediately above the stalk. Because of the multiple origin of the tract which runs into the stalk, Roussy and Mosinger called it the tractus hypothalamohypophyseus instead of the tractus supra-optico-hypophyseus. They traced it into the pars intermedia and into glandular islets in the pars nervosa and supposedly into the pars tuberalis. We are unable to confirm the latter observation, at least in the cat. They observed that the cells of the filiform nucleus send their axons ventrolaterally to form synapses in the supra-optic nucleus. In a recent publication Roussy and Mosinger [31] described in greater detail the fiber connections between the tangential and the filiform nucleus. According to their observations there are tangentioparaventricular as well as paraventriculotangential fibers. The bipolar neurons of the tangential nucleus send one of their prolongations to the tractus hypothalamohypophyseus and the other toward the paraventricular (filiform) nucleus. The bundle of fibers relating the two nuclei has been named the tractus intertangentioparaventricularis by these investigators. They are not certain whether or not some of the fibers pass directly into the stalk without interruption at the supra-optic nucleus. We suggest, in agreement with Roussy and Mosinger, that the bundle of fibers which courses through the ventral wall of the stalk be called the tractus supra-optico-hypophyseus, that the bundle which runs into the dorsal wall be called the tractus tuberohypophyseus and that the two together be designated the tractus hypothalamicohypophyseus.

Development of the Disturbances of Water Metabolism.—The results obtained on forty animals subjected to operation have been selected for presentation at this time. Disturbances of water metabolism developed in twelve of these. In ten instances prolonged and permanent polyuria occurred, and in two cats transient polyuria was

31. Roussy, G., and Mosinger, M.: Les voies d'association homolatérales de l'hypothalamus, Compt. rend. Soc. de biol. **116**:858, 1934.

observed. By reference to tables 1 and 2, it is seen that in seven cats with permanent polyuria a transient diuresis developed which preceded the onset of the permanent phase. The periods of transient polyuria lasted from one to eight days (table 1, column 2) and were followed by intervals during which normal conditions of water exchange

TABLE 1.—*Data Relating to Transient Polyuria in Twelve Cats*

Cat	Duration of Polyuria, Days	Average Urine Output, Cc.	Maximum Urine Output, Cc.	Occurrence of Peak of Polyuria After Operation, Days	Urine Output on First Day of Transient Polyuria, Cc.	Fluid Intake on First Day of Transient Polyuria, Cc.
71	Transient polyuria absent					
74	7	248	360	2	255	280
91	1	165	165	3	165	140
133	3	133	200	1	200	355
162	1	325	325	On day of operation	325	530
166	5	335	600	2	155	130
168	7	288	360	2	300	340
125	8	121	160	6	120	210
106	Data incomplete					
132	Polyuria questionable					
129*	2	625	940	1	940	1,000
135*	2	112	135	1	135	325

* Permanent polyuria did not develop in cats 129 and 135.

TABLE 2.—*Data Relating to Permanent Polyuria in Twelve Cats*

Cat	Period Between Transient and Permanent Polyuria: Average Urine Output, Cc.	Period Between Transient and Permanent Polyuria: Average Fluid Intake, Cc.	Day Before Onset of Permanent Polyuria: Urine Output, Cc.	Day Before Onset of Permanent Polyuria: Fluid Intake, Cc.	Day of Onset of Permanent Polyuria: Urine Output, Cc.	Day of Onset of Permanent Polyuria: Fluid Intake, Cc.	Duration of Latent Period Before Permanent Polyuria, Days
71	68	86	85	100	195	100	12
74	97	100	120	100	290	170	12
91	71	91	65	75	205	100	9
133	52	73	85	100	160	100	12
162	55	73	65	75	145	100	11
166	46	93	50	100	115	100	8
168	Early permanent polyuria; very mild; onset indeterminate						
125	Data incomplete; no permanent polyuria during first 15 days; moderate permanent polyuria detected 1½ months after operation						
132	No permanent polyuria prior to eighteenth postoperative day; cat very sick (anorexia); moderate permanent polyuria detected 1½ months after operation						
106	Data incomplete; moderate permanent polyuria detected 2½ months after operation						
129	No permanent polyuria						
135	No permanent polyuria						

prevailed (table 2, columns 2 and 3). At the end of this period the onset of the permanent phase of the polyuria was observed. In six instances in which the data are complete the interval between the day of operation and the onset of permanent polyuria varied from eight to twelve days (table 2, column 8). We have termed this interval the latent period. One animal, cat 71, with marked permanent polyuria which developed after a latent period of twelve days did not show the early transient polyuria. In cats 106 and 132 moderate permanent polyuria developed which was not detected until some time after opera-

tion, and in these cases we are not certain as to the occurrence of early transient polyuria. In cats 129 and 135 transient polyuria appeared which was not followed by permanent derangement of the water metabolism. In the case of cat 125 permanent polyuria did not develop within the first fifteen days, but moderate polyuria was detected one and one-half months after operation, after the condition had apparently been present for some time. In cat 168 there was well marked transient polyuria, but in the early stages the permanent polyuria was so mild that the precise moment of onset could not be determined. Later this animal showed rather marked diabetes insipidus.

Differences Between the Transient and the Permanent Polyuria.—Several important differences were observed between the transient and the permanent phase of the polyuria. The average output of urine during the transient phase for the nine animals (cats 74, 91, 133, 162, 166, 168, 125, 129 and 135) varied from 112 to 625 cc. (table 1, column 3). In column 4 are given the peak outputs during the transient phase of the polyuria, which varied from 160 to 940 cc., and in column 5 is recorded the postoperative day on which these outputs occurred. For all except two animals (cats 91 and 125) the peak of the output occurred within the first two postoperative days. On the other hand, the permanent phase of the polyuria generally developed much more slowly. After the first increase in the output of urine and the intake of fluid at the end of the latent period, a week or more sometimes elapsed before the polyuria and polydipsia became more or less fixed, and during this period there was a gradual increase in urine output and fluid intake. Thus, in the case of cat 166 a period of ten days elapsed after the onset of the permanent phase before a level of about 400 cc. for the output of urine was established.

It was found that at the onset of the transient polyuria the intake of fluid usually exceeded the output of urine on the first day of the diuresis. This was true in seven of the nine cases (table 1, columns 6 and 7). We do not wish to stress this point unduly, for in certain other cases which we have observed this did not occur. Sometimes in animals which were in a comatose condition on the day after operation, considerable polyuria appeared without the ingestion of fluid. It appears that if the animal is up and about at the time polyuria occurs it is able to take in enough fluid, and in most instances more than enough, to compensate for the diuresis. On the other hand, during the onset of the permanent phase of polyuria the conditions are reversed, and the output of urine is greater than the intake of fluid. In columns 4 and 5 of table 2 the figures for the output of urine and the intake of fluid are listed for six cats on the last day of the latent period before the onset of the permanent polyuria. In five of these cases the intake of fluid exceeded the output of urine, but usually by only a small

amount. In these cases the conditions were reversed on the day of the onset of the permanent phase (columns 6 and 7, table 2), and although the intake of fluid remained constant the output of urine suddenly increased. In the case of cat 74 the output of urine was greater than the intake of fluid on the day before the onset of the permanent polyuria, but on the day on which the onset occurred the excretion of urine was so far in excess of the intake of fluid as to leave no doubt that the polyuria was primary to the polydipsia. After a few days the intake of fluid was observed to be equal to and to exceed the output of urine, and throughout the course of the permanent phase the intake of fluid slightly exceeded the output of urine. It seems clear, then, that during the onset of the permanent polyuria, the polyuria is primary and the polydipsia simply compensatory in character. On the other hand, during the transient phase the polyuria may be primary in some cases, and this is especially clear in an animal in a comatose state. However, since in most instances intake of fluid exceeds the output of urine on the first day, it is not possible to draw definite conclusions as to the primacy of the polyuria.

Another important difference between the transient and the permanent phase is that during the former the urine output and fluid intake may reach proportions never observed in the latter phase. Thus, cat 129 (table 1, column 4) excreted 940 cc. of urine on the first day after operation, and cat 166, 600 cc.; the amount of fluid ingested was proportionate.

Intensity, Duration and General Course of the Permanent Polyuria.—A comparison of tables 3 and 4 gives some idea of the intensity of the permanent polyuria. In table 3 are recorded the output of urine, the specific gravity of the urine and the intake of fluid and of food of twenty-five normal cats, twelve of which were later subjected to operation. Sixteen cats which were limited to 60 Gm. of meat and 100 cc. of milk had an average daily output of 94 cc. of urine, the specific gravity of which was 1.028, and an intake of 94 cc. of fluid. The average consumption of meat was 57 Gm. Eight cats which were limited to 100 Gm. of meat and 100 cc. of milk and another animal receiving a more generous diet showed an average daily output of 98 cc. of urine, the specific gravity of which was 1.029 and an intake of 86 cc. of fluid. The average consumption of meat was 91 Gm. As indicated in table 4, six of the ten animals with permanent polyuria showed a marked increase in water exchange, the output of urine ranging from 218 to 433 cc. and the intake of fluid from 226 to 441 cc. In four cats moderate permanent polyuria developed, the output of urine ranging from 121 to 171 cc. and the intake of fluid from 135 to 171 cc. For all of the animals except cats 71 and 74 the daily intake of food averaged 60 Gm. The figures in the column headed

"Fluid Intake" in table 4 represent the average combined intakes of milk and of water; the amount in excess of 100 cc. represents the amount of water ingested. It was found that normal cats rarely, if ever, drink water, even on the hottest days, and this fact facilitated the detection of small deviations from the normal conditions of water exchange, for whenever an animal began to drink water consistently, even in very small amounts, it could be established that permanent

TABLE 3.—*Average Daily Output of Urine, Specific Gravity and Intake of Food and of Fluid of Twenty-Five Normal Cats*

Cat	Time of Observation, Days	Average Urine Output, Cc.	Specific Gravity of Urine	Average Fluid Intake, Cc.	Average Food Intake, Gm.
Group Limited to 100 Gm. of Meat					
2	15	86	1.034	60	94
3 (Op. 83)*	13	81	1.032	77	90
4	41	100	1.031	100	100
7	9	82	1.027	100	80
8	12	102	1.023	98	71
10	13	134	1.022	98	90
11	6	91	1.026	96	83
12 (Op. 103)	6	122	1.023	96	83
19 (Op. 125)	9	83	1.045	48	135
Averages	..	98	1.029	86	91
Group Limited to 60 Gm. of Meat					
13	4	121	1.028	102	50
14	5	92	1.027	98	40
17 (Op. 94)	6	95	1.025	90	50
18 (Op. 91)	2	92	1.024	85	50
27 (Op. 160)	4	95	1.027	100	60
28 (Op. 159)	2	120	1.030	100	60
30	3	100	1.027	100	60
31	3	103	1.022	100	60
32 (Op. 157)	2	72	1.025	100	60
33 (Op. 158)	6	117	1.025	100	60
34	4	94	1.029	100	60
35 (Op. 166)	6	66	1.036	61	60
36	15	106	1.029	100	60
40	2	50	1.035	70	60
41 (Op. 170)	1	85	1.025	100	60
42 (Op. 168)	1	100	1.028	100	60
Averages	..	94	1.028	94	57

* The numbers in parentheses are those assigned the animals in the operative series.

TABLE 4.—*Average Daily Output of Urine, Specific Gravity and Intake of Food and of Fluid of Ten Cats with Permanent Polyuria*

Cat	Duration of Polyuria	Period of Polyuria Included in Table	Average Urine Output, Cc.	Average Specific Gravity of Urine	Average Fluid Intake, Cc.	Average Food Intake, Gm.
71	2 mos.	2 mos.	303	1.012	304	100
74	2 mos.	2 mos.	379	1.010	387	100
91 (normal cat 18)	9 mos.	7 mos.	372	1.007	375	60
133	6 mos.	5 mos.	433	1.007	441	60
162	2 mos.	5 wks.	150	1.021	135	60
166 (normal cat 35)	4½ mos.	4 mos.	374	1.008	373	60
168 (normal cat 42)	3 mos.	1 mo.	158	1.018	156	60
		2 wks.	218	1.012	226	60
125 (normal cat 19)	6 mos.	1 mo.	171	1.016	171	60
106	8 mos.	9 days	114	1.019	128	60
		1 mo.	125	1.024	158	60
132	7 mos.	1 mo.	121	1.021	147	60

polyuria was present. The urine of the animals with permanent polyuria was pale and watery and of low specific gravity. The specific gravity was proportionate to the intensity of the polyuria. Thus, cat 133 had marked polyuria, and the specific gravity of its urine was 1.007 (table 4, column 5), whereas cat 125 had a moderate polyuria and the specific gravity of its urine was 1.016. The corresponding average value for the specific gravity of the urine of sixteen normal cats on the same diet was 1.028.

Once established, the permanent polyuria persisted until the animal was killed. In the ten diabetic animals the condition lasted for from two to nine months (table 4, column 2), and in no case did it spontaneously disappear. In the case of cat 91 the polyuria and polydipsia persisted for nine months in a marked form, while in cat 133 an even more intense diabetes insipidus was present for six months. On the other hand, in several cases moderate permanent polyuria became somewhat more marked with the passage of time. In this connection cats 125 and 132 and especially cat 168 may be mentioned. There is no reason to think that the experimental polyuria in these cases would not have persisted indefinitely.

The animals with marked polyuria showed daily variations in the output of urine and in the intake of fluid as great as from 100 to 150 cc., but on the whole a fairly constant level was maintained. These animals seldom excreted more than 500 cc. of urine daily, an occasional output of about 600 cc. in the case of cat 91 or cat 133 being the largest amount observed.

Data on Cats in Which Polyuria Did Not Develop.—In table 5 are given the pertinent data for the twenty-eight cats which were operated on without the appearance of polyuria. Many of these animals were in metabolism cages at several different times during the period of their survival, even though but one of the intervals may be represented in column 3 under the heading "Period of Observation." A constant check was made of the intake of the fluid when the animals were not in metabolism cages, so that the absence of polyuria was established with certainty. Most of the casts, also, were replaced in metabolism cages for the days immediately preceding the time of their being killed.

Of the twenty-eight animals in which polyuria did not appear after operation the nine limited to 100 Gm. of meat had an average output of 76 cc. of urine, the average specific gravity of which was 1.033, and an average intake of 88 cc. of fluid. The average consumption of meat was 91 Gm. The remaining nineteen cats which were limited to 60 Gm. of meat, had an average output of 66 cc. of urine, the specific gravity of which was 1.037, an average intake of 79 cc. of fluid and of 50 Gm. of meat. By comparing these values with the corresponding

ones in table 3 for the groups receiving 60 and 100 Gm., respectively, it is noted that in both groups the output of urine was somewhat lower in the case of the animals undergoing operation. Although the nine which were cats operated on in the group receiving 100 Gm. consumed almost the same amount of milk and of meat as the corresponding group of normal animals, the output of urine in the case of the former was, on

TABLE 5.—*Average Daily Output of Urine, Specific Gravity and Intake of Food and Fluid of Twenty-Eight Cats Not Developing Polyuria Following Operation*

Cat	Survival Period	Period of Observation, Days	Average Urine Output, Cc.	Average Specific Gravity of Urine	Average Fluid Intake, Cc.	Average Food Intake, Gm.
Group Limited to 100 Gm. of Meat						
63	2 mos.	4	57	1.030	125	100
65	3 mos.	5	82	1.023	100	100
67	1 mo.	10	45	1.045	32	100
70	1½ mos.	31	77	1.034	86	96
72	2 mos.	27	95	1.037	100	100
75	1 mo.	30	81	1.036	85	83
76	1½ mos.	27	99	1.033	100	88
83 (normal cat 3)	1½ mos.	28	80	1.030	72	70
84	5 wks.	33	71	1.030	93	88
Averages	.....	..	76	1.033	88	91
Group Limited to 60 Gm. of Meat						
69	1½ mos.	21	62	1.044	70	55
77	2 mos.	20	23	1.052	27	34
90	8 mos.	35	61	1.023	87	4
94 (normal cat 17)	6 mos.	20	98	1.031	100	60
96	4 mos.	6	85	1.029	100	60
103 (normal cat 12)	9 mos.	11	66	1.042	77	60
115	3 mos.	22	45	1.048	65	46
116	8 mos.	56	82	1.030	100	60
117	3 mos.	54	68	1.036	89	56
157 (normal cat 32)	4 mos.	15	67	1.037	83	60
158 (normal cat 33)	4 mos.	40	89	1.031	98	60
159 (normal cat 28)	4 mos.	34	70	1.037	77	60
160 (normal cat 27)	1 mo.	27	41	1.039	28	42
161	4 mos.	3	90	1.029	100	60
169	3 mos.	9	54	1.047	76	40
170 (normal cat 41)	3 mos.	25	73	1.032	86	53
172	2½ mos.	64	66	1.031	69	60
174	16 days	15	47	1.041	102	23
175	3 wks.	17	60	1.041	90	60
Averages	.....	..	66	1.037	79	50

the average, more than 20 cc. less, and the specific gravity, 0.004 higher. A possible explanation for the discrepancy is that the figures for the output of urine of the cats operated on included, in most instances, the values obtained during the period of convalescence.

Effect of Deprivation of Water and Food on Polyuria.—Several experiments which we carried out indicate clearly that when animals with polyuria are deprived of water but are given the normal ration of food (100 cc. of milk and 60 Gm. of meat), a marked reduction in the output of urine occurs and the excretion eventually reaches a normal level if the deprivation of water is continued for a sufficiently long time. Thirst experiments of this type were carried out on cats 91

and 133, both of which had marked permanent polyuria. In table 6 are recorded the results of the experiments.

It is evident that in the two cases the output of urine decreased rapidly and approached normal values, while the specific gravity rose considerably. Although the output of urine tended to approach normal values, the water balance in each case was still considerably on the negative side. If 90 cc. is accepted as the normal output of urine for cat 91 on this diet, which is the amount it excreted in its normal state, there was a total loss of 115 cc. of fluid from the organism in the period of three days. Applying the same criterion to cat 133, it may be seen that there was a total loss of fluid of 140 cc. in a period of two days. It is interesting to note that in the two cats the loss of fluid was made up on the day after the deprivation of water was discontinued. Thus, on the day after the experiment cat 91 drank 160 cc. more fluid than

TABLE 6.—*Effect of Deprivation of Water on Polyuria in Two Cats*

Cat	Urine Output on Day Before Thirst Experiment, Cc.	Urine Output During Thirst Experiment, Cc.			Average Fluid Intake, Milk, During Thirst Experiment, Cc.	Negative Balance of Water Exchange, Cc.	Day After Experiment		Positive Balance of Water Exchange, Cc.
		First Day	Second Day	Third Day			Urine Output, Cc.	Fluid Intake, Cc.	
91	350 (1.008)*	165 (1.011)	120 (1.020)	105 (1.021)	100	115	425 (1.005)	585	160
133	455 (1.008)	175 (0.014)	145 (1.020)	...	100	140	500 (1.005)	615	115

* Figures in parentheses indicate specific gravity.

it excreted, and cat 133, 115 cc. more, whereas the output of urine and the intake of fluid approximated one another much more closely during the ordinary course of the polyuria. When the animals were given water after the cessation of the experiment, they immediately and avidly drank large amounts of it. For example, cat 133 drank over 200 cc. in a period of about one and one-half hours.

When the animals with marked polyuria were given a free supply of water but were deprived of meat and milk, there was also a marked decrease in the urinary output. The day before the deprivation of food in the case of cat 166 the output of urine was 425 cc., the specific gravity, 1.005, and the intake of fluid, 425 cc. During the experiment the urine output decreased to 150 cc., the specific gravity, to 1.006, and the fluid intake, to 130 cc. Similar results were obtained for cat 91. In each instance the specific gravity of the urine remained about the same during as before the period of starvation.

Effect of Pitressin on Experimental Diabetes Insipidus.—Injections of pitressin into two animals caused a marked reduction in the fluid

exchange. As shown in table 7, the results obtained with cats 91 and 133 indicate that the output of urine and the intake of fluid were reduced almost to normal levels and that they then increased to the preinjection values on the day after the injections were discontinued. The injections were made subcutaneously, 1 cc. being given to cat 91 on each of two days in several small doses at frequent intervals, and 2 cc. per day similarly administered to cat 133, in which the polyuria was more intense.

Lesions Which Produce Diabetes Insipidus.—Microscopic examination of the serial sections of the brains of the ten animals with experimental diabetes insipidus has shown consistently that the disorder arises only if bilateral injury to the supra-optico-hypophyseal system is present. In none of these cases was there direct destruction of the supra-optic nuclei, but the axons of the cells of the nuclei, which make up the tractus supra-optico-hypophyseus, were interrupted at various points between the supra-optic nuclei and the posterior lobe.

TABLE 7.—*Effect of Pitressin on Polyuria in Two Cats*

	Day Before Injections		First Day of Injections		Second Day of Injections		Day After Injections	
Cat	Urine Output, Cc.	Fluid Intake, Cc.	Urine Output, Cc.	Fluid Intake, Cc.	Urine Output, Cc.	Fluid Intake, Cc.	Urine Output, Cc.	Fluid Intake, Cc.
91	315 (1.008)*	350	210 (1.015)	170	105 (1.027)	100	355 (1.008)	325
133	485 (1.006)	520	240 (1.015)	225	120 (1.023)	140	455 (1.008)	450

* Figures in parentheses indicate specific gravity.

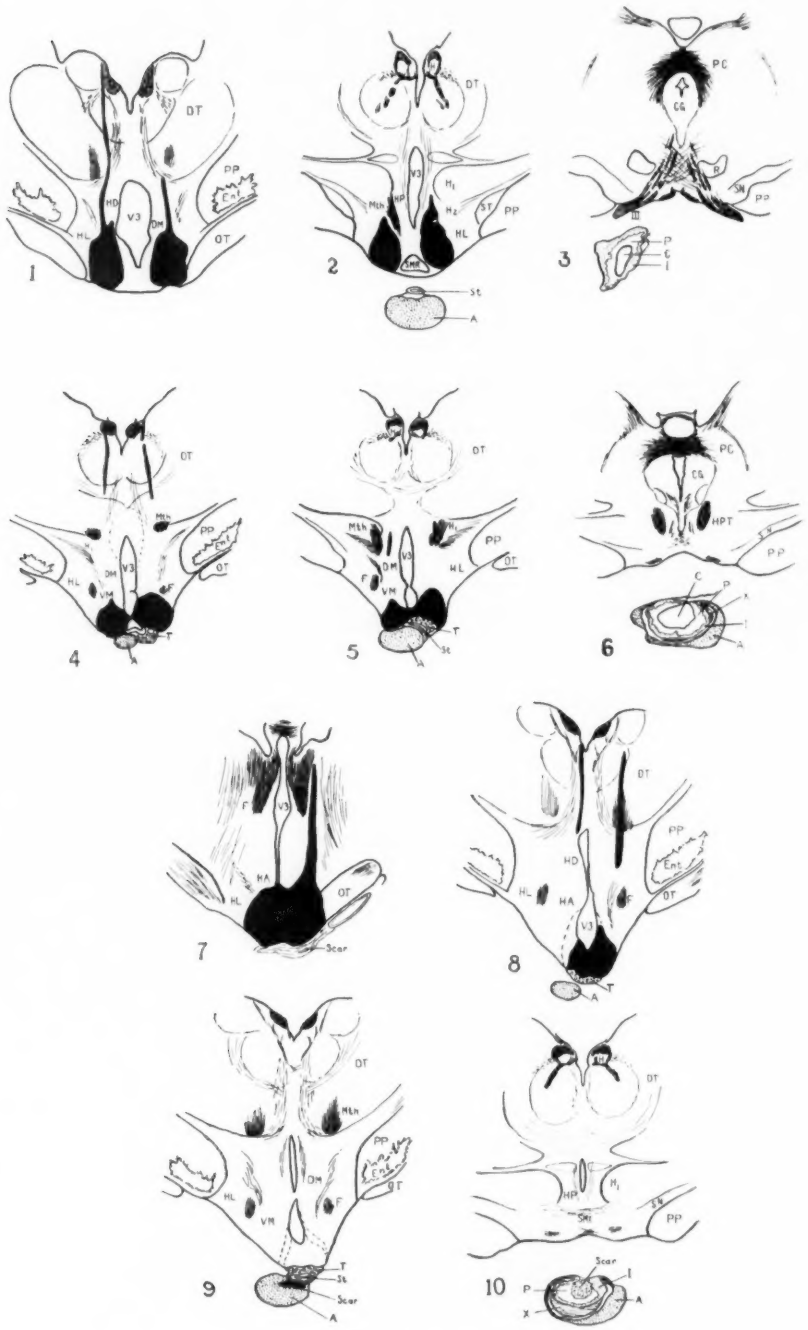
In three instances (cats 71, 106 and 166) the interruption occurred through lesions placed between the optic chiasma and the rostral end of the pituitary stalk, in such a position that they destroyed the greater part of the anterior and ventromedial hypothalamic nuclei. Such a lesion occurring in cat 71 is shown in figure 32. In each case the lesions extended to the base of the tuber and destroyed the superficially coursing supra-optico-hypophyseal tract. In three cats (74, 91 and 162) the destruction of the tractus supra-optico-hypophyseus took place in part by lesions similar to those just described, but also through interruption of its fibers as a result of damage to the pituitary stalk. In two instances (cats 132 and 133) injury to the stalk was the chief factor responsible for the interruption of the fibers of this system.

In each of the ten cats the supra-optic nuclei were more or less atrophied; that is, there was a marked decrease in size owing to the diminution in the number of cells. In most instances only a few cells were left. A striking example of such an atrophy may be seen by comparing the photograph of the atrophic supra-optic nucleus of cat 74 in figure 31 with the normal supra-optic nucleus in figure 30.

In each animal there was atrophy of the posterior lobe of the hypophysis, with enlargement of the cavity of the posterior lobe and of the interglandular cleft. The atrophic posterior lobe of cat 74 is shown in figure 34, with which may be compared a normal posterior lobe shown in figure 35. The atrophy was marked in all the animals except cat 168, in which it was moderate (fig. 22). Atrophic posterior lobes are illustrated in figures 3, 6, 10, 13, 16, 22, 25 and 28. It is to be observed that the atrophy consisted of an enlargement of the cavity of the posterior lobe and a thinning of the walls not only of the posterior lobe but of the stalk. The thinning of the walls of the stalk is well shown in figure 27. The entire pars neuralis appeared to be shrunken, and as a consequence the interglandular cleft was larger than the normal. The pars intermedia seemed to be histologically normal, but in each case it was to be observed to be wrinkled and folded to accommodate itself to the shrinkage of the posterior lobe (fig. 28). The nuclei of the pars neuralis were greatly increased in density. We are not certain whether the peculiar glia-like cells observed in the nervous portion of the pituitary body and called pituicytes by Bucy [30] are involved in this increase. The pituicytes can be seen in sections of normal tissue of the posterior pituitary gland, stained by Penfield's modification of the del Rio-Hortega silver carbonate stain. In a similar preparation of an atrophic posterior lobe, the cells with long processes and the dense meshwork of glial fibers appeared to be absent. Instead, there were large numbers of elongated black-staining cells without processes. We are not certain whether these represent pituicytes which have lost their processes. For brevity, in the protocols we have referred to this change as an increase in the density of the pituicytes. In addition, there is a marked proliferation of connective tissue, as compared with the normal pars nervosa, which is apparent in sections stained by Van Gieson's method. An interesting formation, which was observed to surround and encapsulate the pars intermedia in these animals with polyuria (figs. 34 and 25 *x*), was a ring of colloid-like material which stained dark blue with cresyl violet and dark yellow with Van Gieson's stain. The ring was noted only in the animals in which permanent polyuria developed.

A brief description of the lesions produced in these cats and the accompanying diagrams of the sections will serve to particularize the general statements already made. In the diagrams the lesions are indicated by solid black areas.

CAT 71.—The tractus supra-optico-hypophyseus was interrupted by the lesions shown in figures 1 and 32, which destroyed the anterior hypothalamic nuclei. The lesions extended through the ventromedial part of the hypothalamus to the rostral part of the mamillary bodies and to the very base of the hypothalamus in such a manner as to interrupt the superficially placed tractus supra-optico-hypophyseus. The supra-optic nuclei were markedly atrophic, and the filiform nuclei also showed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Figs. 1 to 10

EXPLANATION OF FIGURES 1 TO 10

Figs. 1 to 3.—Diagrams of sections through the hypothalamus of cat 71: *1*, through the region of the anterior hypothalamic nuclei; *2*, through the posterior part of the hypothalamus just rostral to the mamillary bodies, and *3*, through the mesencephalon, showing the atrophic posterior lobe of the hypophysis. The abbreviations used in this figure and the accompanying figures are as follows: *A*, pars anterior of hypophysis; *C*, cavity of posterior lobe; *CG*, central gray matter of aqueduct; *DM*, dorsomedial nucleus of hypothalamus; *DT*, dorsal thalamus; *Ent*, entopeduncular nucleus; *F*, fornix; *Fil*, filiform (paraventricular) nucleus; *GX*, Ganser's commissure; *H*, habenula; H_1, H_1, field of Forel; H_2, H_2, field of Forel; *HA*, anterior hypothalamic area; *HD*, dorsal hypothalamic area; *HL*, lateral hypothalamic area; *HP*, posterior hypothalamic nucleus; *HPT*, habenulopeduncular tract; *I*, pars intermedia of hypophysis; *L*, lesion; *M*, mamillary body; *Mth*, mamillothalamic tract; *MX*, Meynert's commissure; *OT*, optic tract; *P*, pars neuralis of hypophysis; *PC*, posterior commissure; *Perivent*, periventricular nucleus; *PP*, pes pedunculi; *R*, red nucleus; *SMR*, submamillary recess; *SMX*, supramamillary decussation; *SN*, substantia nigra; *St*, stalk of hypophysis; *ST*, subthalamic nucleus; *T*, pars tuberalis of hypophysis; *Tang*, tangential (supraoptic) nucleus; *V*, blood vessel; *VM*, ventromedial hypothalamic nucleus; *V3*, third ventricle; *X*, colloid-like ring; *III*, oculomotor nerve.

Figs. 4 to 6.—Diagrams of sections through the hypothalamus of cat 74: *4*, through the region of the ventromedial hypothalamic nuclei; *5*, at the level of the anterior lobe of the pituitary, and *6*, through the mesencephalon, showing the atrophic posterior lobe.

Figs. 7 to 10.—Diagrams of sections through the hypothalamus of cat 91: *7*, at the level of the anterior hypothalamic nuclei; *8*, through the rostral end of the floor of the pituitary stalk; *9*, through the anterior lobe of the pituitary at the level of the ventromedial hypothalamic nuclei, and *10*, through the posterior portion of the hypothalamus, showing the atrophic posterior lobe.

considerable atrophy. In figure 2 are shown the caudal continuation of the lesion just rostral to the mamillary bodies and the intact anterior lobe of the pituitary gland. The pars tuberalis was completely intact. Figure 3 shows the markedly atrophic posterior lobe with its enlarged cavity and the wrinkled and folded pars intermedia. Several masses of colloid-like material were found around the pars intermedia. The glial nuclei in the pars neuralis were increased in density.

Cat 74.—The tractus supra-optico-hypophyseus was interrupted by the lesions shown in figure 4; the lesion on the right destroyed the ventromedial hypothalamic nucleus, and on the left the interruption occurred partly at the level of the ventromedial nucleus and partly by direct damage to the pituitary stalk. At this point the pars tuberalis and the rostral end of the anterior lobe of the pituitary gland were also damaged. The supra-optic nuclei were markedly atrophic (fig. 31) as compared with the normal (fig. 30), and the filiform nuclei were moderately so. In figure 5 the lesions are shown a little farther caudal, and the integrity of the greater part of the pars anterior and the pars tuberalis of the hypophysis is evident. The pronounced atrophy of the posterior lobe is shown in figures 6 and 34. The great enlargement of the cavity of the posterior lobe, the wrinkling of the pars intermedia, the widening of the interglandular cleft and the formation of a colloid-like ring around the pars intermedia are obvious. The glial nuclei in the pars neuralis showed an increase in density.

Cat 91.—The supra-optico-hypophyseal tract was interrupted between the optic chiasma and the stalk by the lesions shown in figures 7 and 8. The lesions destroyed the anterior hypothalamic areas and the rostral part of the ventromedial nuclei and extended into the floor of the stalk. The supra-optic nuclei were markedly atrophic, and the filiform nuclei showed moderate atrophy. The rostral part of the pars tuberalis was injured, and a definite scar in the pars anterior indicated injury (fig. 9). The posterior lobe showed pronounced atrophy (fig. 10), accompanied by wrinkling and folding of the pars intermedia. A heavy colloid-like mass surrounded the latter, and the density of the pituicytes was increased. The cavity of the posterior lobe was completely obliterated by a scar formation containing what appeared to be connective tissue.

Cat 106.—The tractus supra-optico-hypophyseus was interrupted by the lesions in the anterior and ventromedial hypothalamic nuclei shown in figures 11 and 12. The supra-optic nuclei showed pronounced, and the filiform nuclei moderate, atrophy. The pars tuberalis and the anterior lobe of the pituitary gland were intact (figs. 12 and 13). The entire posterior region of the hypothalamus was spared. Figure 13 shows marked atrophy of the posterior lobe, accompanied by the usual enlargement of the cavity, wrinkling of the pars intermedia, widening of the interglandular cleft and deposition of a heavy ring of colloid. The density of the pituicytes was increased.

Cat 132.—The tractus supra-optico-hypophyseus was interrupted by direct damage to the pituitary stalk and the floor of the third ventricle just rostral to the stalk (fig. 14). The lower part of the ventricle, the floor of the stalk and the submamillary recess were greatly distended (figs. 14 and 15). The supra-optic nuclei showed marked, and the filiform nuclei moderate, atrophy. The anterior lobe was directly damaged, as shown by the scar in figure 15. Figure 16 shows the pronounced atrophy of the posterior lobe, enlargement of the cavity, widening of the interglandular cleft and folding and wrinkling of the pars intermedia. There was an increase in the density of the pituicytes, and a definite ring of colloid was present.

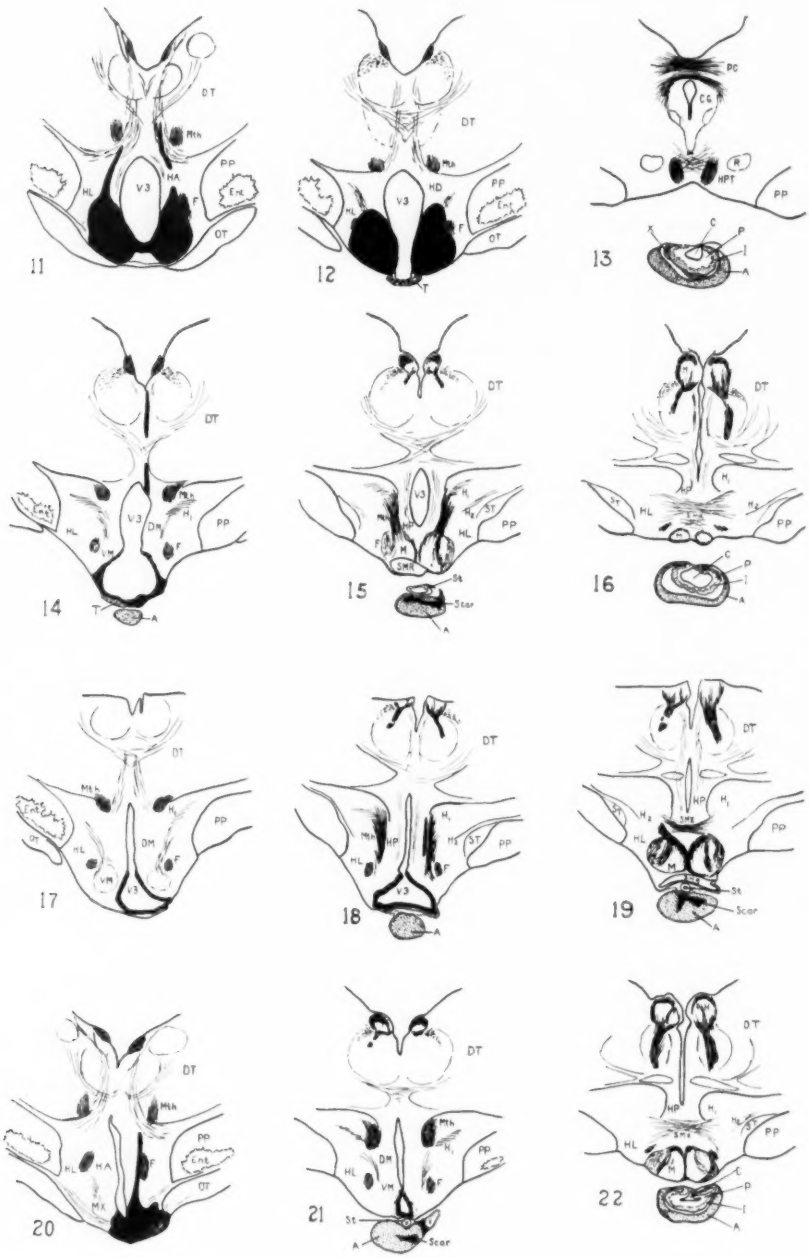
CAT 133.—The tractus supra-optico-hypophyseus was interrupted in the pituitary stalk itself. The lower part of the ventricle and the stalk were markedly distended (figs. 17 and 18). The rostral part of the floor of the stalk was very thin and was closed by a narrow strand of tissue (fig. 17). The actual damage to the hypothalamus was slight except for the erosion of the walls of the lower part of the ventricle in the region of the stalk. The submamillary recess also showed marked distention. The supra-optic nuclei showed pronounced atrophy, and the filiform nuclei were only slightly atrophic. The same lesions that injured the stalk directly damaged the anterior lobe, as shown by the large scar in figures 19 and 33. The posterior lobe was torn during removal, but from the remnants which were saved it was evident that there were marked atrophy, enlargement of the cavity, wrinkling of the pars intermedia, an increase in the density of the pituicytes and the deposition of a colloid ring.

CAT 162.—The supra-optico-hypophyseal tract was partially interrupted by the lesions in the anterior hypothalamic areas, as shown in figure 20. There may also have been direct damage to the stalk, for the ventricle was somewhat distended in this region (fig. 21), and the needle electrode had penetrated the stalk and damaged the anterior lobe (fig. 21). The supra-optic nuclei showed moderate atrophy. In figure 22 is shown moderate atrophy of the posterior lobe with an accompanying moderate increase in the size of its cavity, widening of the interglandular cleft and folding and wrinkling of the pars intermedia. The pituicytes showed increased density. A mass of colloid-like material was found in the cavity of the posterior lobe, but none was present about the pars intermedia.

CAT 166.—The supra-optico-hypophyseal tract was interrupted by the lesions shown in figures 23 and 24. The lesions damaged the optic chiasma and tracts and the anterior and ventromedial hypothalamic nuclei. The supra-optic nuclei were markedly atrophic, while the filiform nuclei were moderately so. The rostral part of the pars tuberalis and perhaps the rostral tip of the anterior lobe of the pituitary were slightly damaged. The atrophy of the posterior lobe is shown in figure 25. There were enlargement of the cavity, widening of the interglandular cleft, folding of the pars intermedia and the deposition of a heavy colloid ring. The pituicytes were increased in density.

CAT 168.—The tractus supra-optico-hypophyseus was partially interrupted by the lesions in the anterior hypothalamic area just medial to the optic tract, as shown in figure 26. The greater part of the lesion damaged the anterior lobe, as indicated in figure 27. The lesions also appear to have damaged the stalk, not directly but through a secondary inflammatory process. The pars tuberalis was partially injured. The posterior lobe showed marked atrophy (fig. 28) with the usual enlargement of the cavity, widening of the cleft, folding of the pars intermedia and increase in the density of the pituicytes. No colloid ring was present.

CAT 125.—The sections were difficult to interpret. The chief lesions were in the postinfundibular region, apparently in a position to interrupt the fibers running into the dorsal wall of the stalk. In the ventral floor of the stalk there was a peculiar formation consisting of a skein of what appeared to be myelinated fibers. We have never observed myelinated fibers in the stalk in other animals. It is possible that the fibers were misplaced nerve tissue (pseudoheterotopia). The supra-optic nuclei were moderately atrophic, probably owing to the interruption of the supra-optico-hypophyseal tract in the region of the skein of fibers just described. The posterior lobe showed the most pronounced degree of atrophy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Figs. 11 to 22

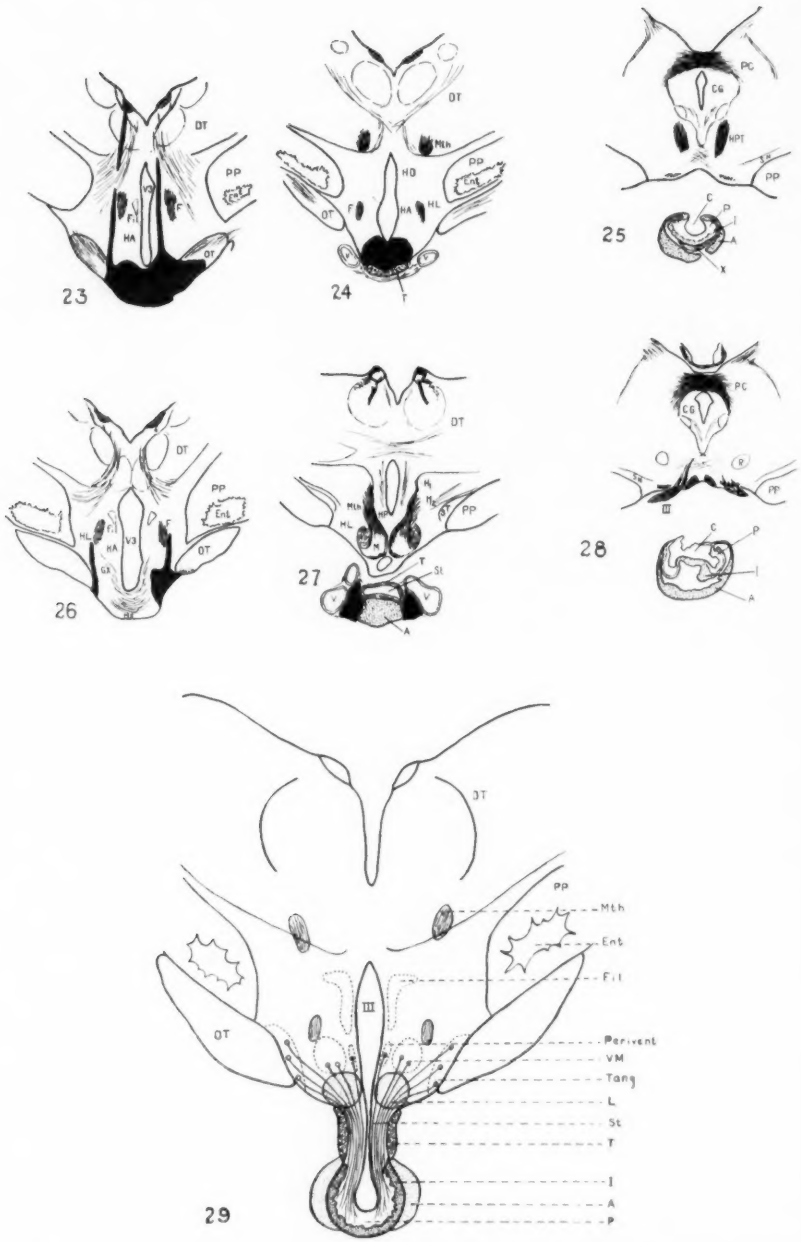
EXPLANATION OF FIGURES 11 TO 22

Figs. 11 to 13.—Diagrams of sections through the hypothalamus of cat 106: *11*, through the anterior hypothalamic nuclei; *12*, at the level of the ventromedial hypothalamic nuclei, and *13*, through the mesencephalon, showing the atrophic posterior lobe.

Figs. 14 to 16.—Diagrams of sections through the hypothalamus of cat 132: *14*, at the level of the ventromedial hypothalamic nuclei; *15*, through the posterior part of the hypothalamus and the anterior lobe of the pituitary, and *16*, through the posterior part of the hypothalamus, showing the atrophic posterior lobe.

Figs. 17 to 19.—Diagrams of sections through the hypothalamus of cat 133: *17*, at the level of the ventromedial hypothalamic nuclei; *18*, through the posterior part of the hypothalamus and the anterior lobe of the pituitary, and *19*, through the posterior part of the hypothalamus, the mamillary bodies and the anterior lobe of the pituitary.

Figs. 20 to 22.—Diagrams of sections through the hypothalamus of cat 162: *20*, at the level of the anterior hypothalamic nuclei; *21*, through the ventromedial hypothalamic nuclei and the anterior lobe of the pituitary, and *22*, through the posterior part of the hypothalamus, showing the atrophic posterior lobe.



Figs. *23* to *25*.—Diagrams of sections through the hypothalamus of cat 166: *23*, through the anterior hypothalamic nuclei; *24*, at the level of the rostral part of the stalk and the pars tuberalis, and *25*, through the mesencephalon, showing the atrophic pars neuralis.

Figs. *26* to *28*.—Diagrams of sections through the hypothalamus of cat 168: *26*, through the anterior hypothalamic region; *27*, through the posterior part of the hypothalamus and the anterior lobe of the pituitary, and *28*, through the mesencephalon, showing the atrophic posterior lobe.

Fig. *29*.—Diagram of the supra-optico-hypophyseal system. The stippled areas just beneath the ventromedial hypothalamic nuclei indicate one of the positions in which lesions must be placed in order to produce diabetes insipidus. Only the caudal parts of the supra-optic nuclei are shown.

which we have seen. Only a narrow rim of tissue of the pars neuralis and an extremely large cavity were left. The pars intermedia was reduced in width and was surrounded by a colloid ring. The marked atrophy of the posterior lobe may have been due in part to the interruption of the tuberohypophyseal tract in the dorsal wall of the stalk.

In table 8 the kind and the degree of polyuria observed in the different animals are summarized and correlated with the condition found in the supra-optic nuclei and in the hypophysis. It is to be noted that in six cases (cats 71, 74, 91, 133, 166 and 168) in which marked

TABLE 8.—*Correlation of the Type of Polyuria with the Condition of the Supra-Optic Nuclei and of the Hypophysis*

Cat	Transient Polyuria	Permanent Polyuria	Supra-Optic Nuclei	Anterior Lobe	Posterior Lobe	Intermediate Lobe
71	None	Marked	Marked atrophy	No lesion	Marked atrophy	Wrinkling and folding; colloid ring
74	Marked	Marked	Marked atrophy	Lesion	Marked atrophy	Wrinkling and folding; colloid ring
91	Slight	Marked	Marked atrophy	Lesion	Marked atrophy	Wrinkling and folding; colloid ring
133	Moderate	Marked	Marked atrophy	Lesion	Marked atrophy	Wrinkling and folding; colloid ring
162	Marked	Moderate	Moderate atrophy	Lesion	Moderate atrophy	Colloid in cavity of posterior lobe; wrinkling and folding
166	Marked	Marked	Marked atrophy	Slight lesion	Marked atrophy	Colloid ring; wrinkling and folding
168	Marked	Marked	Marked atrophy	Lesion	Marked atrophy	No colloid ring; wrinkling and folding
125	Moderate	Moderate	Moderate atrophy	Lesion	Very marked atrophy	Very thin colloid ring
106	?	Mild	Marked atrophy	No lesion	Marked atrophy	Wrinkling; colloid ring
132	?	Moderate	Marked atrophy	Lesion	Marked atrophy	Wrinkling; colloid ring
129	Very marked	None	Normal	Lesion	Normal	Normal
135	Moderate	None	Normal	Lesion	Normal	Normal

permanent polyuria developed, the supra-optic nuclei and the posterior lobe showed pronounced atrophy. In cat 162 there was moderate permanent polyuria accompanied by moderate atrophy of the posterior lobe and of the supra-optic nuclei. In cats 106 and 132, although only mild permanent polyuria occurred, the supra-optic nuclei and the posterior lobe were markedly atrophic. However, the figures in table 4 for cat 132 do not give a fair estimate of the intensity of the polyuria if the intake of water is taken as a measure of the degree of derangement in the exchange of fluid, for in the later stages of polyuria, the amount of water drunk daily amounted to more than 100 cc. The output of urine was decreased because of the cat's refusal to consume much milk. In cat 125 in which there developed moderate permanent polyuria, the supra-optic nuclei showed moderate atrophy but the posterior lobe was markedly atrophic. It is to be seen, therefore, that

although in seven cats the degree of polyuria was proportional to the extent of the atrophy of the supra-optic nuclei and of the posterior lobe in three cases the correlation did not hold true.

In regard to the two animals (cats 129 and 135) which had transient polyuria not followed by the permanent phase, the important damage appears to have been done to the anterior lobe, whereas the supra-optico-hypophyseal system was intact. We have been considerably puzzled as to the explanation of the transient polyuria which preceded the onset of permanent diabetes insipidus, but at the present time the evidence is not complete enough for definite conclusions. However, since in cats 129 and 135 the principal damage was done to the anterior lobe of the pituitary, it seemed probable that the transient polyuria was caused by an irritative lesion of this division of the pituitary, especially in view of other considerations to be discussed shortly. In cats 74, 91, 133, 162, 166, 168 and 125 (table 8) transient polyuria occurred, and in each case damage to the anterior lobe or to the pars tuberalis was present. Figure 33 shows a large lesion in the anterior lobe of the pituitary in cat 133. No correlation existed between the degree of the damage to the anterior lobe and the intensity of the transient polyuria. Thus, in cat 91 a very mild, even questionable, transient polyuria occurred, but there was a rather marked lesion of the anterior lobe (fig. 9). On the other hand, cat 166 showed a marked and prolonged transient polyuria, whereas there were slight damage to the pars tuberalis and a questionable injury to the rostral tip of the anterior lobe. The case of cat 71, however, seems to confirm the interpretation already given of the origin of the transient polyuria, for in this animal there was no early transient diuresis, and the pars tuberalis and the anterior lobe were intact (figs. 2 and 32). Unfortunately, our evidence is deficient in just this respect; the only other permanently diabetic animal with the anterior lobe intact was cat 106. This animal, however, was taken out of the metabolism cage two days after operation, and, although we have a complete record of the intake of fluid, the record of the output of urine during the early stages is complete for the first two days only. During this period there was no polyuria, although on the second day 70 cc. of water was drunk; during the next few weeks no water was consumed. We are reluctant, therefore, to draw conclusions from this case. Another animal (cat 132) had a decided lesion of the anterior lobe (fig. 15), but it is questionable whether transient polyuria developed. The first day after operation, before the cat was placed in a metabolism cage, it drank 25 cc. of water and urinated twice, but the urine was not collected. We are, therefore, uncertain whether or not to call this case one of mild transient polyuria. Because of the discrepancies in our data and the absence of other cases of the type shown by cat 71, the question as to the etiology of the transient polyuria

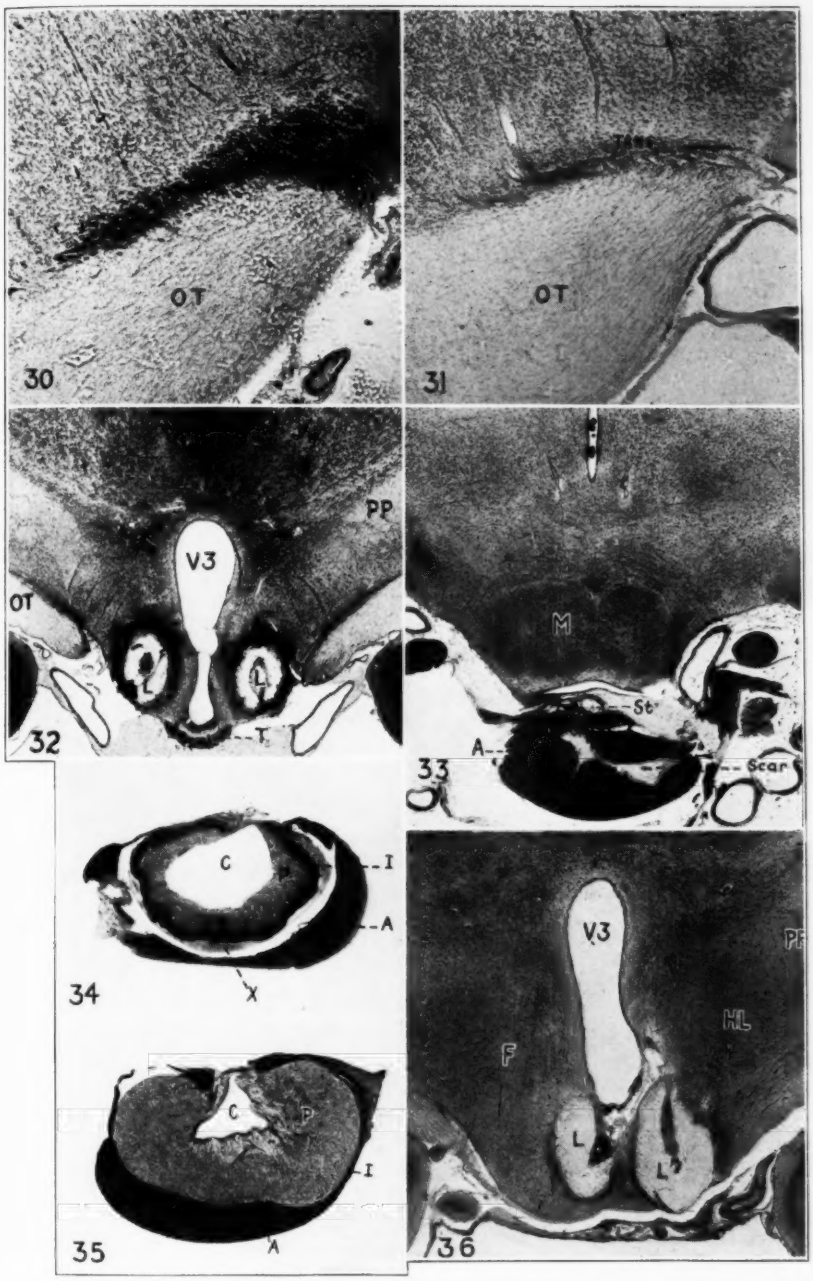


Fig. 30.—Photomicrograph of a normal supra-optic nucleus.

Fig. 31.—Photomicrograph of the atrophic supra-optic nucleus of cat 74.

Fig. 32.—Photomicrograph of the lesions in the anterior hypothalamic areas in cat 71 which produced diabetes insipidus. The pars tuberalis is intact.

Fig. 33.—Photomicrograph of the lesion of the anterior lobe in cat 133.

Fig. 34.—Photomicrograph showing the atrophic posterior lobe of cat 74.

Fig. 35.—Photomicrograph showing a normal posterior lobe.

Fig. 36.—Photomicrograph showing the lesions in cat 72 in which unilateral atrophy of the supra-optic nucleus occurred. The lesion on the left does not reach the base of the tuber.

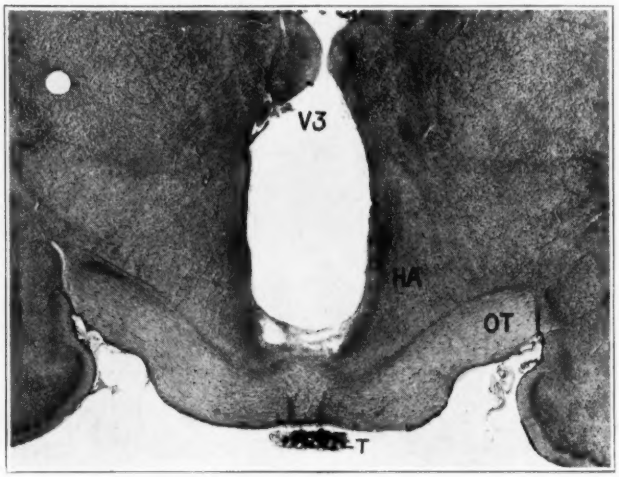


Fig. 37.—Photomicrograph showing the destruction of the filiform nuclei in cat 174. The lesions destroyed the wall of the third ventricle for a depth of about 1 mm. on each side.

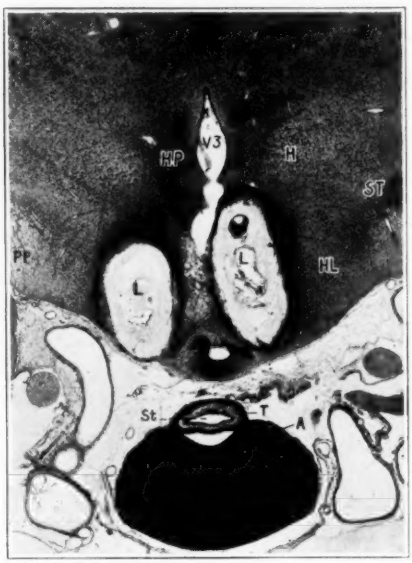


Fig. 38.—Photomicrograph showing the lesions in cat 83 which destroyed the posterior part of the hypothalamus just rostral to the mamillary bodies. The normal stalk and anterior lobe of the pituitary are normal.

should be left open. We are at present carrying out further experiments designed to test the hypothesis that the anterior lobe plays a part in the regulation of water metabolism.

The twenty-eight animals operated on in which polyuria did not develop confirm, by the negative evidence that they present, the observation that the destruction of the supra-optico-hypophyseal system causes diabetes insipidus. Unilateral destruction of this system does not bring about a derangement of water metabolism. In figure 36 are shown the lesions produced in cat 72. It is to be noted that on the right the lesion in the anterior hypothalamic area reached to the base and was in a position to interrupt the supra-optic fibers. On this side, the atrophy of the supra-optic nucleus was marked. On the left the lesion did not extend to the base, and the supra-optic nucleus was intact. The case is an excellent illustration of the precision with which the lesions must be placed in order to produce polyuria, for if the lesion on the left had extended less than a millimeter farther ventrad permanent polyuria would undoubtedly have developed in this animal. The posterior lobe in this cat was considerably atrophied and the cavity was enlarged, whereas the walls of the stalk on the right were very thin. Several other animals (cats 75 and 76) have shown partial unilateral destruction of the tractus supra-optico-hypophyseus without the intervention of polyuria.

The remaining cases in which negative results were obtained may be summarized briefly. A composite picture of the lesions in these cats would undoubtedly include the entire hypothalamus, with the exception of the supra-optic nuclei and of the tract arising from them. We have noted in the description of the lesions in the cats with permanent polyuria that in almost every case the filiform nuclei showed some degree of atrophy, in spite of the fact that the lesions were considerably removed from them. This suggests that fibers from the cells of these nuclei join the tractus supra-optico-hypophyseus, as Greving [23d] and as Roussy and Mosinger [16] have suggested. Nevertheless, our results indicate that the destruction of the filiform nuclei alone is not sufficient to cause polyuria. Figure 37 shows the lesions in cat 174, in which the filiform nucleus was completely destroyed on each side. The lesions destroyed the wall of the third ventricle for a depth of several millimeters on each side. Polyuria did not develop in this animal, although for the first week or so after operation it drank about 25 cc. of water daily. Figure 38 shows the lesions in another animal (cat 83) without polyuria, in which the lesions were in the posterior part of the hypothalamus; not one of the many animals with lesions of this type has indicated the slightest tendency toward polyuria. Other animals without polyuria showed complete and partial destruction of the mamillary bodies, the lateral hypothalamic and perifornical areas, the ventrolateral hypothalamic nucleus and so on.

It does not appear necessary that other hypothalamic nuclei be destroyed with the supra-optico-hypophyseal system in order to produce polyuria. Thus, although in most of the cases of permanent polyuria there was more or less destruction of the anterior and ventromedial hypothalamic nuclei, in cats 132 and 133 the nuclei were largely spared. Moreover, in many animals, as in cat 72, the nuclei were destroyed without the intervention of polyuria. Neither does it seem necessary that there be an accompanying destruction of some of the posteriorly lying nuclei, as occurred in cats 71 and 74, for in cats 106 and 166 this region was intact.

We have been somewhat puzzled as to why the destruction of the fibers which course down the dorsal wall of the stalk does not result in marked atrophy of the posterior lobe. We have pointed out that the dorsal bundle is smaller and is composed of finer fibers than is the ventral tract, and this fact may account for the apparent absence of atrophy. Moreover, it may have a larger area of origin than has the ventral bundle, which would necessitate the destruction of a very large region before all of the fibers are involved. In cat 125, although there was only moderate atrophy of the supra-optic nuclei, the posterior lobe showed greater atrophy than was observed in any other animal; only a very narrow rim of tissue of the pars neuralis remained. The lesions were in a position to interrupt the fibers coursing into the dorsal wall of the stalk and were very large, destroying much of the posterior part of the hypothalamus. As we have pointed out, however, this was a peculiar case, and the atrophy may have been due to other causes, especially since in cats with similar lesions (e. g., cat 90) no such atrophy was observed. It has been our impression that many of the animals in which polyuria did not develop showed enlargement of the cavity of the posterior lobe as compared with normal animals, and this may represent a mild atrophy due to the cutting off of fibers of the tractus hypothalamico-hypophyseus other than those of the supra-optico-hypophyseal bundle.

The failure to produce complete atrophy of the posterior lobe in animals with permanent polyuria may have been due to the persistence of fibers in the pars neuralis which pass by way of the dorsal wall of the stalk. Studies are now in progress to determine more definitely the disposition of the fibers of the posterior lobe following hypothalamic lesions.

COMMENT

We have presented a considerable mass of evidence which demonstrates conclusively that bilateral injury to the supra-optico-hypophyseal tract results in diabetes insipidus and that such injury is accompanied by atrophy of the posterior lobe of the hypophysis. In other words, we have shown that the diencephalic-hypophyseal mechanism postulated

by many investigators in recent times plays a rôle in the regulation of water metabolism. There is little evidence in the literature in support of this view. The best work is probably that of Broers,[3] who produced a polyuria of one year's duration in one dog by direct bilateral destruction of the supra-optic nucleus. In our cases we did not produce direct injury of this type. It was found possible to elicit permanent polyuria by a much smaller lesion placed between the optic chiasma and the pituitary stalk in such a way that the fibers of the tractus supra-optico-hypophyseus were interrupted just before the point where they collect into a bundle to pass down the stalk. We have pointed out that the supra-optic nucleus covers a considerable area and is divided into several portions; in order to destroy it in its entirety a very large lesion would therefore be necessary. In another animal Broers produced polyuria by interruption of the tractus supra-optico-hypophyseus in the floor of the stalk. This investigator also observed marked atrophy of the posterior lobe in one of his animals, and unilateral atrophy of the posterior lobe in another following unilateral destruction of the supra-optico-hypophyseal system. In the latter animal, as in cat 72 in our series, permanent polyuria did not develop.

Aside from the work of Broers, the only other experimental evidence tending to implicate the supra-optico-hypophyseal system is that of Maddock (Cushing[4]), who produced permanent polyuria by placing a silver clip on the pituitary stalk in a dog and later demonstrated the absence of nerve fibers distal to the point of attachment of the clip.

From the clinical side there is support for our observations. Lewy[32] and Cassirer and Lewy[33] noted atrophy of the supra-optic and filiform nuclei in several patients with diabetes insipidus. The most interesting case is that of Kiyono;[34] he observed atrophy of the two nuclei and an accompanying atrophy of the posterior lobe. Curtis[35] noted a similar atrophy of the posterior lobe in dog F 15 of his series. The nature of the hypophyseal atrophy does not seem to have been taken into consideration by previous workers. We have shown that in the cat it consists of an enlargement of the cavity of the pars neuralis and a thinning of the walls of the posterior lobe, accompanied either by a genuine increase of the number of glial nuclei or by an apparent increase due to the shrinkage of the posterior lobe. Just what

32. Lewy, F. H.: Pathologischanatomische Befunde bei Diabetes insipidus, Klin. Wchnschr. **1**:2500, 1922.

33. Cassirer, R., and Lewy, F. H.: Zur Differentialdiagnose der hypophysären Geschwülste, Monatschr. f. Psychiat. u. Neurol. **54**:267, 1923.

34. Kiyono, H.: Ueber Zwischenhirnveränderungen bei Diabetes insipidus, Virchows Arch. f. path. Anat. **257**:477, 1925.

35. Curtis, G. M.: The Production of Experimental Diabetes Insipidus, Arch. Int. Med. **34**:801 (Dec.) 1924.

is represented by the colloid-like mass which we observed encapsulating the pars intermedia we cannot state. The pars intermedia appears to be normal in structure, but it is wrinkled and folded to accommodate itself to the shrinkage of the posterior lobe. It is our opinion that the enlargement of the cavity of the pars neuralis and the reduction in size of the pars itself are due to the degeneration of the fibers of the tractus supra-optico-hypophyseus which have been interrupted in the hypothalamus or in the stalk and which normally form a dense meshwork in the posterior lobe or end in the pars intermedia itself. The presence of the cavity in the posterior lobe in the cat makes atrophy of the lobe readily detectable; the absence of such a cavity in other animals may account for the failure of other investigators, with the exception of Broers, to note atrophy of this structure.

All of the evidence cited indicates the correctness of Cushing's assumption that injury to the supra-optico-hypophyseal system at any one of three points, namely, the nucleus, the fiber tract, or the pars neuralis and pars intermedia, should cause diabetes insipidus. Broers has proved this assumption for the injury to the supra-optic nucleus; we have done so for that of the fiber tract, as did Richter [12] in his experiments on the separation of the stalk, and there is a great deal of clinical and experimental evidence which relates the posterior and the intermediate lobe to diabetes insipidus.

The superficial course of the supra-optico-hypophyseal tract along the base of the tuber cinereum has not been emphasized by previous investigators. We are of the opinion that this location is of importance, for it offers a plausible explanation for the development of diabetes insipidus as a result of various pathologic conditions at the base of the tuber cinereum. For example, Fink [36] reported, on the basis of an analysis of one hundred and seven necropsies in cases of diabetes insipidus, that in 13 per cent the lesion was due to a syphilitic process, either to basal meningitis or to gummas in or near the hypophysis; in 6 per cent the lesion was a tuberculoma or tuberculous meningitis of the base, while in 8 per cent the condition was due to a nonsyphilitic inflammatory process in the same location.

Frank [37] and others have postulated that the pars tuberalis possesses an antidiuretic function and is able to assume the rôle of the posterior lobe following so-called total hypophysectomy. Our results provide no support for this contention. In two of the permanently diabetic animals

36. Fink, E. B.: Diabetes Insipidus: A Clinical Review and Analysis of Necropsy Reports, Arch. Path. **6**:102 (July) 1928.

37. Frank, E.: Ueber die Beziehungen von Hypophyse und Thalamus zum Wasseraushalt, Med. Klin. **25**:699, 1929.

(cats 71 and 106) the pars tuberalis was completely intact, showing that diabetes insipidus may occur in the presence of a normal pars tuberalis.

An examination of the observations of earlier workers who attempted to elicit polyuria by means of hypothalamic lesions reveals that in each case the lesions were in a position to injure the supra-optico-hypophyseal system, although at that time the existence of such a system was not known. Thus, Camus and Roussy [38] insisted that a superficial lesion in the preinfundibular region was sufficient to cause polyuria. In Bailey and Bremer's [39] dog 10 the important damage appears to have been, not the postinfundibular lesion as they thought, but the detachment of the posterior lobe from the infundibulum. In the case of dog F 15 in Curtis' [35] series the important lesion was in the floor of the stalk, and in Richter's [40] experiments on rats the lesions were made in the preinfundibular region.

Our results fail completely to confirm the view of Bourquin [41] that diabetes insipidus is due to the release of a diuretic substance as a consequence of irritation to the mamillary bodies. We have observed many cases of partial and several cases of complete destruction of this region without having observed an accompanying polyuria in any case.

An examination of the published figures and graphs of other investigators relating to the output of urine and the intake of fluid in animals with polyuria has brought to light in several instances the occurrence of the early transient polyuria which we found to precede the permanent phase of the polyuria, although none of these workers has made a distinction between the transient and the permanent phase. Moreover, in a number of cases the latent period before the onset of the permanent phase was about as long as in our own animals. Thus, in the case of dog F 15 in Curtis' [35] series, the output of urine rose to a peak of 2,500 cc. on the second day after the operation and then gradually declined until the preoperative level of about 200 cc. was reached nine days after operation. On the tenth day the permanent phase of the polyuria began. Dog 10 in Bailey and Bremer's [39] series showed a simi-

38. Camus, J. and Roussy, G.: Les fonctions attribuées a l'hypophyse, J. de physiol. et de path. gen. **20**:509 and 535, 1922.

39. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

40. Richter, C. P.: Experimental Diabetes Insipidus, Brain **53**:76, 1930.

41. Bourquin, H.: (*a*) Studies on Diabetes Insipidus: I. Am. J. Physiol. **79**: 362 (Jan.) 1927; (*b*) Studies on Diabetes Insipidus: II. The Diuretic Substance: Preliminary Observations, ibid. **83**:125 (Dec.) 1927; (*c*) Further Observations on the Diuretic Substance of Experimental Diabetes Insipidus, ibid. **85**: 354 (June) 1928; (*d*) Studies on Diabetes Insipidus: III. The Diuretic Substance: Further Observations, ibid. **88**:519 (April) 1929; (*e*) Studies on Diabetes Insipidus: IV. ibid. **96**:66 (Jan.) 1931.

lar transient polyuria which subsided and was followed by the onset of permanent polyuria on the eleventh day. One of Camus and Roussy's [42] dogs showed transient polyuria followed by permanent polyuria after a latent period of ten days, and Broer's [3] dog 16 showed a similar course with a latent period of ten days. From the clinical side it is, of course, impossible to determine the length of the latent period in cases of diabetes insipidus of pathologic origin. However, Ciminata [43] reported a case of diabetes insipidus of traumatic origin which first became manifest twelve days after the injury. We do not wish to stress unduly the relative constancy of the latent period (from eight to twelve days) which we observed in our animals, for in a new series of cats now under observation we have seen a case in which permanent polyuria did not develop until sixteen days after operation. We are of the opinion that the long latent period indicates rather clearly that diabetes insipidus is due to a destructive rather than to an irritative lesion.

The statements in the literature with regard to the primacy of the polyuria or of the polydipsia are somewhat conflicting. The French school (Roussy and Mosinger [9]) has always maintained that the polyuria is primary, and this view has been supported by Bourquin [41] and by Leschke.[10] Curtis,[35] on the other hand, found that polydipsia precedes polyuria, and Richter [40] was able to demonstrate that the peak of the daily intake of fluid in animals with polyuria precedes that of the output of the urine. Our own results show that during the onset of the permanent phase of polyuria the output of urine first becomes excessive and is followed by a compensatory increase in the intake of fluid; they thus indicate the primacy of the polyuria. We are of the opinion that the conflicting reports in the literature on this point are due, in part at least, to the failure to distinguish between the transitory and the permanent phase of the polyuria, for, as will be remembered, the primacy of the polyuria cannot be observed in most cases during the transient period. The question of the primacy of the polyuria is important with regard to the theory that diabetes insipidus is due to a deficiency of the secretion of the antidiuretic principle by the pars neuralis or by the pars intermedia. For if the antidiuretic hormone acts directly on the kidney, as the best evidence seems to indicate (Macdonald [44] and Burgess, Harvey and Marshall [45]), and prevents it from excreting too

42. Camus, J., and Roussy, G.: Polyurie expérimentale permanente, Compt. rend. Soc. de biol. **83**:764, 1920.

43. Ciminata, A.: Sulla regolazione idrica e salina nell'uomo, in rapporto al diabete insipido da trauma cranico, Fisiol. e med. **2**:641, 1931.

44. Macdonald, A. D.: The Action of Pituitary Extracts on the Kidney, Quart. J. Exper. Physiol. **23**:320, 1933.

45. Burgess, W. W.: Harvey, A. M., and Marshall, E. K., Jr.: The Site of the Anti-Diuretic Action of Pituitary Extract, J. Pharmacol. & Exper. Therap. **49**:237, 1933.

much water, a deficiency of the hormone would be expected to bring about primary polyuria followed by compensatory polydipsia. In this connection, our experiments on deprivation of water are of interest. The fact that deprivation of water decreases the polyuria is not, in our opinion, a valid argument that the polydipsia is primary, as Curtis [35] has claimed. What is of greater importance is that, in spite of the marked fall in the output of urine to a practically normal level after about three days of thirst, there is a considerable loss of fluid from the organism during the period of water deprivation, during which the output of urine exceeds the intake of fluid. After several days, the dehydration reaches a point at which, in the absence of free water, the urine output balances the fluid intake. As soon as the animal is given a free supply of water, it immediately makes up the loss of fluid sustained during the thirst experiment.

In considering the rôle of the supra-optico-hypophyseal system in diabetes insipidus it is necessary to determine whether this system carries afferent or efferent impulses. The anatomic studies which we have listed in a previous section indicate that one is dealing here with an efferent tract, and the work of Maddock (Cushing [4]) on the degeneration of the fibers distal to a clip placed on the stalk tends to confirm this opinion. The atrophy of the supra-optic nuclei and of the posterior lobe after hypothalamic lesions observed by Broers [3] and by ourselves is further evidence in favor of the theory of an efferent system. Certain physiologic experiments also point in this direction. Schürmeyer [46] elicited a positive reaction of the melanophores in the skin of a frog after stimulation of the tuber cinereum, which was presumably due to the activation of the pars intermedia. Karplus and Peczenik [47] observed an outpouring of intermedin into the cerebrospinal fluid after stimulation of the tuber cinereum.

The most logical interpretation of the way in which injury of the supra-optico-hypophyseal system brings about polyuria is that such an injury results in the cutting off of secretory impulses from the supra-optic nuclei to the pars posterior and the pars intermedia and brings about a deficiency of the antidiuretic principle which is secreted by one or the other of these two divisions of the hypophysis. Just where the antidiuretic hormone is elaborated is not known at the present time, but recent work suggests that the pars intermedia is the site of formation.

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46. Schürmeyer, A.: Ueber die Innervation der Pars intermedia der Hypophyse der Amphibien, Klin. Wchnschr. **5**:2311, 1926.

47. Karplus, J. P., and Peczenik, O.: Ueber die Beeinflussung der Hypophysentätigkeit durch Erregung des Hypothalamus, Arch. f. d. ges. Physiol. **232**:402, 1933.

Sulzberger [48] and Turner (in a personal communication) reported that they had successfully treated diabetes insipidus with preparations of Zondek and Krohn's [49] hormone, intermedin, which is extracted from the pars intermedia. This is of interest in connection with the experiments of Karplus and Peczenik already noted. Ferguson [50] isolated a specific water-regulating principle from crude extracts of the middle lobe of the pituitary and has given it the name aquamedin. Ferguson stated (in a personal communication) that this preparation represents a pure antidiuretic fraction and is distinct from the hormones of the posterior lobe and from intermedin. He has used it successfully in the treatment of ten patients with diabetes insipidus. It may be suggested that the colloid-like formation which we have observed encapsulating the pars intermedia in most of the diabetic cats is caused by a disturbance of the secretory activity of this part of the hypophysis.

The results which we obtained with injections of pitressin confirm those of Bailey and Bremer [39] and of Broers,[3] who likewise observed a diminution in the intensity of the polyuria and polydipsia of diabetes insipidus after treatment with pituitary extracts. The fact that this disorder may be successfully treated by means of extracts of the posterior and intermediate lobes is in itself an argument in favor of the theory that it is due to a deficiency in the secretion of the antidiuretic hormone by these divisions of the hypophysis. On the other hand, Bailey and Bremer [39] and Leschke [10] have maintained that the antidiuretic action of these preparations represents no more than an interesting pharmacologic property. This argument does not seem convincing in the light of the following chain of circumstances: The only hypothalamic lesions which produce diabetes insipidus are those which injure the supra-optico-hypophyseal system and bring about changes in the posterior and the intermediate lobe; the tractus supra-optico-hypophyseus innervates the pars intermedia, and extracts of the latter have been shown to possess antidiuretic properties. These facts furnish suggestive evidence in favor of the theory of deficiency, but up to the present time such a deficiency has not been conclusively demonstrated.

A number of investigators have attempted to show a deficiency of posterior pituitary-like substances in the cerebrospinal fluid of patients with diabetes insipidus, but these experiments have taken the form of measuring the oxytocic and the melanophore-expanding properties of the

48. Sulzberger, M. B.: The Pituitary Hormone Intermedin as the Active Antidiuretic in the Treatment of Diabetes Insipidus: Preliminary Report, J. A. M. A. **100**:1928 (June 17) 1933.

49. Zondek, B., and Krohn, H.: Hormon des Zwischenlappens der Hypophyse (Intermedin), Klin. Wchnschr. **11**:405, 849, and 1293, 1932.

50. Ferguson, R. S.: Aquamedin for Diabetes Insipidus, Mod. Med. **2**:27, 1934.

fluid rather than the antidiuretic properties. Janossy and Magoss [51] found an absence of uterus-contracting substance in the cisternal fluid of patients with diabetes insipidus. They considered this observation evidence of the hypophyseal origin of this disease and held that the secretion of the posterior lobe passed into the third ventricle. Leschke [10] and Hoff and Wermer [52] were not able to confirm this observation, but the last two investigators found that whereas normal persons showed an increase in the content of posterior pituitary-like substance of the cerebrospinal fluid after the administration of a diuretic, aminophylline, persons with polyuria failed to respond in this way.

As we have shown, the only hypothalamic lesions which produce experimental polyuria are those which affect the posterior and intermediate hypophyseal lobes. This observation suggests that in the last analysis diabetes insipidus is a hormonal disorder. In favor of this view the work of Verney [53] may be mentioned. This investigator found that when the head and neck of a dog are perfused in parallel with the kidney of a heart-lung-kidney preparation a marked inhibition of the diuresis normally occurring in such a preparation ensues. Extirpation of the hypophysis from the head of the dog led to the return of polyuria. He concluded that the copious flow of dilute urine from the isolated kidney is due to the absence of the hypophyseal secretions from the circulation. Further evidence for the hormonal theory has been provided by Compère [13] and by Brull,[14] who showed that the hypochloruria and polyuria accompanying hypophysectomy are transmissible through the blood stream to the kidneys of a normal dog by way of the carotid-jugular circulation.

Negative evidence in favor of the hormonal origin of diabetes insipidus in the sense that it does not represent a nervous disturbance has accumulated in the literature. Houssay and Carulla,[54] Bailey and Bremer [39] and Camus and Gournay [55] have shown that denervation of the kidneys does not interfere with the development or the course

51. Janossy, J., and Magoss, F.: Angaben über die Funktion der menschlichen Hypophyse, Wien. klin. Wchnschr. **43**:1201, 1930.

52. Hoff, V. H., and Wermer, P.: Untersuchungen über die Beeinflussung der Pituitrinsekretion durch Diuretica, Klin. Wchnschr. **6**:1180, 1927.

53. Verney, E. B.: The Secretion of Pituitrin in Mammals as Shown by Perfusion of the Isolated Kidney in the Dog, Proc. Roy. Soc., London, s. B **99**: 487, 1926. Verney, E. B.: Goulstonian Lectures on Polyuria: I. Polyuria Associated with Pituitary Dysfunction, Lancet **1**:539 (March 16) 1929.

54. Houssay, B., and Carulla, J. E.: Polyurie par piqûre cérébrale chez les chiens á reins énervés, Compt. rend. Soc. de biol. **83**:1252, 1920.

55. Camus, J., and Gournay, J. J.: La polyurie tubérienne après énervation des reins, Compt. rend. Soc. de biol. **88**:694, 1923.

of experimental polyuria of hypothalamic origin. Rubio [56] found that section of the splanchnic nerves, removal of the abdominal sympathetic chain or section of both vagi failed to interfere with the production of experimental polyuria. Bourquin [41a] showed that transection of the cord at the upper thoracic or the lower cervical level and double vagotomy below the diaphragm failed to influence the development or the course of experimental polyuria. She showed further [41e] that transection of the brain stem behind the mamillary bodies had no effect on the production of polyuria, and hence that descending pathways from the hypothalamus were not involved. Finally, Janssen [57] demonstrated that transection of the cervical cord or of the brain stem at the level of the colliculi failed to abolish the antidiuretic effect of the hormone of the posterior lobe of the hypophysis.

As has been noted, we have been somewhat puzzled as to the explanation of the early transient phase of polyuria. It may be incorrect to separate the early phase from the permanent phase as a distinct phenomenon. We have pointed out, however, that it is not a constant occurrence, being absent in cat 71 and perhaps in cat 106. A possible explanation is that there is an immediate effect of shock from the lesions which cut off secretory impulses to the posterior and the intermediate lobe and that this is accompanied by transient polyuria. Following this transient phase there is a partial recovery lasting until the gradual onset of the permanent phase. However, if this explanation were tenable it would be expected that transient polyuria would occur in all of the cases of permanent polyuria and even in the cases of partial injury to the supra-optico-hypophyseal system. Moreover, our results differ from those of previous investigators in that isolated transient polyuria, as in cats 129 and 135, was infrequent. This suggests that not the hypothalamic injury but some other factor is responsible for the transient polyuria. We have suggested the possibility that irritative lesions of the anterior lobe may be responsible for the early polyuria, and we have pointed out that with the operative technics employed by previous workers who have reported transient polyuria so frequently (Bailey and Bremer [39]) irritation of the anterior lobe could hardly have been avoided. It should be noted that in our twenty-eight animals in which the anterior lobe was completely spared transient polyuria did not occur. In addition to this evidence, the differences we have noted between the transient and the permanent phase, namely, the greater rapidity of onset,

56. Rubio, H. H.: Polyurie et atrophie génitale par lésion tubérienne ou hypophysectomie chez des chiens normaux ou sans innervation sympathique, Compt. rend. Soc. de biol. **97**:589, 1927.

57. Janssen, S.: Ueber die Bahnen der zentralen Wasserregulation und der Hypophysen antidiurese, Klin. Wchnschr. **7**:1680, 1928.

the greater intensity and the differences in the relations of output of urine and intake of fluid in the transient phase suggest that a different mechanism is at work which may involve, not a hormonal deficiency but the release of substances which promote diuresis. It may be remarked that the notion that the anterior lobe is involved in the diuresis goes back to the transplantation experiments of Crowe, Cushing and Homans,[58] who showed that transplants of the anterior lobe result in marked diuresis and the removal of the transplants in its cessation. Von Hann,[59] on the basis of clinical evidence which has since been confirmed by numerous investigators, concluded that the anterior lobe secretes diuretic substances antagonistic to the antidiuretic hormone of the posterior lobe. Without going further into the evidence for this view, it may be pointed out that several recent investigators (Teel;[60] Barnes, Regan and Bueno;[61] Biasotti,[62] and others) have been able to produce an enormous diuresis in dogs by the administration of extracts of the anterior lobe.

After it is shown that the supra-optico-hypophyseal system is concerned in the regulation of water metabolism and that the theory of the hypothalamic and that of the hypophyseal origin of diabetes insipidus may be reconciled, the problem of the relation of the hypothalamus and the pituitary gland to water metabolism is by no means completely solved. Several facts stand in the way of the complete acceptance of the hormonal theory. First, there seems to be general agreement that complete hypophysectomy does not result in permanent polyuria, and second, transient polyuria has been elicited by Camus and Roussy,[63] by Houssay, Carulla and Romana[64] and by Warner[65] by hypothalamic puncture after previous hypophysectomy. These findings suggest that

58. Crowe, S. J.; Cushing, H., and Homans, J.: Effects of Hypophyseal Transplantation Following Total Hypophysectomy in the Canine, Quart. J. Exper. Physiol. **2**:389, 1909.

59. von Hann, F.: Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus, Frankfurt. Ztschr. f. Path. **21**:337, 1918.

60. Teel, H. M.: Diuresis in Dogs from Neutralized Alkaline Extracts of the Anterior Hypophysis, J. A. M. A. **93**:760 (Sept.) 1929.

61. Barnes, B. O.; Regan, J. F., and Bueno, J. G.: Is There a Specific Diuretic Hormone in the Anterior Pituitary? Am. J. Physiol. **105**:559, 1933.

62. Biasotti, A.: Thyröide et action diurétique de l'extrait anté-hypophysaire, Compt. rend. Soc. de biol. **115**:329, 1934.

63. Camus, J., and Roussy, G.: Polyurie expérimentale par lésions de la base du cerveau: la polyurie dite hypophysaire, Compt. rend. Soc. de biol. **75**:628, 1913.

64. Houssay, B.: Carulla, J. E., and Romana, L.: Polyurie par piqûre cérébrale chez le chien normal et chez le chien privé d'hypophyse, Compt. rend. Soc. de biol. **83**:1250, 1920.

65. Warner, F. J.: Histopathology of Experimental Diabetes Insipidus, J. Nerv. & Ment. Dis. **73**:375, 1931.

factors other than the influence of the supra-optico-hypophyseal system are involved in the regulation of water metabolism. This suggestion is borne out by the fact that in several of our animals the intensity of the polyuria was not proportional to the degree of injury to the supra-optico-hypophyseal system.

SUMMARY AND CONCLUSIONS

With the aid of the Horsley-Clarke stereotaxic instrument, lesions were placed in various parts of the hypothalamus in forty adult cats. In ten instances prolonged and permanent polyuria developed, while in two cats transient polyuria was observed. In seven of the cats with permanent polyuria transient diuresis which preceded the onset of the permanent phase occurred. The transient polyuria was followed by an interval during which normal conditions of water exchange prevailed. In six instances the interval between the day of operation and the onset of the permanent polyuria varied from eight to twelve days. This interval has been called the latent period.

The transient polyuria has been found to differ from the permanent polyuria in the following respects: It develops much more rapidly and reaches a peak much sooner than does the permanent polyuria; the polyuria is primary to the polydipsia during the permanent phase, while the intake of fluid usually exceeds the output of urine on the first day of the transient phase; during the transient phase the output of urine and the intake of fluid may reach proportions never observed in the permanent phase.

The polyuria and polydipsia in the ten diabetic cats lasted from two to nine months and appeared to be permanent. The output of urine and the intake of fluid for the animals with the most severe diabetes insipidus were five or six times greater than the values for control animals. As the polyuria increased in intensity the specific gravity of the urine became correspondingly lower. Deprivation of water for several days brought about a reduction in the output of urine to a normal level, and deprivation of food resulted in a reduction of the output to about one-half the previous level. During the course of the experiments on the deprivation of water, the animals lost considerable fluid and a negative water balance developed, suggesting that the polyuria is primary. Repeated small doses of pitressin injected subcutaneously caused a reduction in the urine output and the fluid intake to normal levels.

Permanent polyuria was found to occur only in the cases in which there was bilateral injury to the supra-optico-hypophyseal system. Such injury resulted in marked atrophy of the supra-optic nuclei and marked

atrophy of the posterior lobe. Unilateral damage to this system did not cause polyuria, nor did lesions in any of the other parts of the hypothalamus. The possibility that transient polyuria may be related to irritative lesions of the anterior lobe was discussed.

The evidence from this investigation supports the theory that diabetes insipidus is a hormonal disturbance, caused by a deficiency in the secretion of the antidiuretic principle by the posterior or the intermediate lobe of the pituitary gland. The view is set forth that the supra-optico-hypophyseal system sends secretory impulses to these divisions of the hypophysis and that damage to this system at one of three points, the nucleus, the fiber tract and the pars intermedia and pars neuralis, results in diabetes insipidus.

Clinical Notes

A CASE OF EXTENSIVE CALCIFICATION IN THE BRAIN

Selective Calcification of the Finer Cerebral Blood Vessels

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WITH THE TECHNICAL ASSISTANCE OF DOROTHY E. NOBLE AND ANNETTE C. RIVARD

HOWARD, R. I.

Deposits of mineral salts in the brain are found in association with many diseases of the central nervous system. Frequent sites of calcification are tumors originating in the brain and meninges. The deposition of calcium in association with intracranial angiomas, described by Krabbe,[1] Eaves [2] and others, is of especial interest. Such deposits are not uncommon in association with intracranial hematomas; an unusual case of this type was reported recently by Levin.[3] Calcification in association with encephalitis in man was first described by Buzzard and Greenfield [4] and later by Cobb [5] and others. Da Fano and Perdrau [6] found both pseudocalcification and true deposition of calcium in cases of experimental herpetic meningo-encephalitis in rabbits. Carbon monoxide poisoning may be followed by calcification of the media of arteries within three days.[7] Hurst [8] found deposition of mineral salts in arteries of the basal ganglia in many inflam-

From the State Hospital for Mental Diseases.

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1. Krabbe, K. H.: Anatomicopathologic Study of Calcifications in Brain of Patient with Meningeal Angiomas; Relation to Roentgenographically Diagnosed Calcified Angiomas of Meninges, Rev. neurol. **1**:1394 (June) 1932.

2. Eaves, E. C.: Deposits Containing Calcium and Iron in Brain, Brain **49**:307 (Sept.) 1926.

3. Levin, J. J.: Intracerebral Calcification, Brit. J. Surg. **14**:215 (Oct.) 1926.

4. Buzzard, E. F., and Greenfield, J. G.: Lethargic Encephalitis; Its Sequelae and Morbid Anatomy, Brain **42**:305 (Jan.) 1920.

5. Cobb, S.: Vascular Lesions in a Case of Chronic Encephalitis Lethargica with Parkinson's Syndrome, Arch. Neurol. & Psychiat. **16**:240 (Aug.) 1926.

6. Da Fano, C., and Perdrau, J. R.: Chronic or Subacute Herpetic Meningo-Encephalitis in Rabbits with Observations on Calcification, J. Path. & Bact. **30**:67 (Jan.) 1927.

7. Kaufmann, Edward: Pathology for Students and Practitioners, translated by Stanley P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 1898.

8. Hurst, E. W.: So-Called "Calcification" in the Basal Ganglia of the Brain, J. Path. & Bact. **29**:65, 1926.

matory and degenerative diseases of the nervous system. He demonstrated iron in these so-called "calcifications" of the basal ganglia, but was unable to establish the presence of calcium in many of the lesions by the application of suitable tests. Depositions of lime salts are common in the cerebral arteries. Spielmeyer [9] divided arterial calcification in the brain into two types: (1) that involving the media and (2) that beginning in the adventitia, with spread to the media later. Such lesions are most common after middle life, but may be found at any age. Thompson and Piney [10] described calcification of the arteries in the brain of an infant 6 months of age. Ostertag [11] reported two such cases in children 2½ and 3½ years of age, respectively. Mallory,[12] Pick,[13] Bassoe and Hassin,[14] Geyelin and Penfield [15] and others described extensive calcification of the finer cerebral vessels in an interesting group of cases. Mallory's [12] patient died in a general hospital without any abnormal mental symptoms having been noted during life. The observations at necropsy were: chronic nephritis, cardiac hypertrophy, endarteritis, suppurative parotitis, bronchopneumonia, calcification of the arteries of the brain and calcareous concretion in the cerebellum. Microscopically, the process was one of colloid infiltration of the smaller arteries, precapillaries and capillaries by lime salts in a ground substance of colloid material. The arteries at the base of the brain were not involved in the process. Mallory reviewed the literature and found reports of three similar cases. One of the patients was considered normal mentally; one was an idiot, and one was an epileptic. In the case of Bassoe and Hassin [14] there were convulsive seizures which began at the age of 30 in a business man. Later, there were focal neurologic signs suggestive of tumor of the brain. The brain showed lesions of the finer cerebral blood vessels similar to those described by Mallory. Geyelin and Penfield [15] reported a series of cases of intracerebral calcification demonstrated by encephalograms in a father and all three of his children. A portion of the brain of one child was removed surgically, and the lesion was found to be one of calcification of the smaller cerebral blood vessels. The veins were not extensively involved in any of the cases cited.

A case of extensive calcification in the brain, which belongs to the group of calcification of the finer cerebral blood vessels, was studied by one of us (J. Kasamin) for several months before the death of the patient. Studies of the brain and all the other organs of the body were made at necropsy.

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9. Spielmeyer, quoted by Hurst.[8]

10. Thompson, A. P., and Piney, A.: A Case of Decerebrate Rigidity in an Infant Associated with Diffuse Softening of the Cerebral Cortex and Calcification of the Cerebral Vessels, Lancet **2**:1105 (Nov. 26) 1921.

11. Ostertag, B.: Concretions of the Brain, Virchows Arch. f. path. Anat. **275**:828, 1930.

12. Mallory, F. B.: A Contribution to the Study of Calcareous Concretions of the Brain, J. Path. & Bact. **3**:110, 1896.

13. Pick, A.: Calcification of the Finer Cerebral Vessels with Remarks upon Its Clinical Significance, Am. J. Insanity **61**:417, 1905.

14. Bassoe, P., and Hassin, G. B.: Calcification of the Cerebral Vessels with a Clinical Picture Simulating Brain Tumor, Arch. Neurol. & Psychiat. **6**:359 (Oct.) 1921.

15. Geyelin, H. R., and Penfield, W.: Cerebral Calcification Epilepsy: Endarteritis Calcificans Cerebri, Arch. Neurol. & Psychiat. **21**:1020 (May) 1929.

REPORT OF CASE

History.—R. M., a man aged 32, was admitted to the State Hospital for Mental Diseases on Sept. 1, 1927, because for the past ten years he had gradually lost interest in work, had become absent-minded, irritable and impulsive and had attacked some neighbors. Nothing is known about the grandparents. The patient's father, who was rather lazy and irresponsible, was a plumber. The mother was extremely addicted to alcohol. The patient was the twelfth of seventeen children, only five of whom are living. One sibling died in the World War, another died of pernicious anemia at the age of 30, and the others died when very young. All the living siblings are dull intellectually; one sister has paralysis of one side of the body and looks and behaves somewhat like the patient.

Nothing is known about the early history of the patient. He is said to have been a healthy child. He went to grammar school and was considered bright by his family. His health had always been good. The patient stated that he had had a fall ten years before and struck his head, but this was not known to the other members of the family. In spite of the fact that the family considered him bright, he was thought by neighbors to be rather dull and able to get along by doing only odd jobs and menial work. He was never able to hold a position for any length of time and could do only simple tasks. He was much interested in Boy Scouts, associating with them a great deal, and was interested in hiking and farming. He was greatly attached to his mother. There is no history of any acute respiratory infection or any illness which could be interpreted as an attack of encephalitis.

At the age of 22 he suddenly had some convulsive seizures at his mother's funeral. These lasted for several days, and he was in bed for about a week. After the seizures he lost interest in work, as well as in outside activities. He worked in the garden of a cousin and read a little. He became absent-minded, forgot to put out the gas and left the water running until the bathroom was flooded. He became irritable and impulsive. If any one opposed him, he would throw things at his opponent. When he was 30 his father died, and he became even more unmanageable. He had another series of convulsions at that time. He began to throw stones at persons and chased them on the streets and refused to let any one come into the yard. The neighbors became afraid of him.

Examination.—On admission the patient talked slowly; his speech was thick, and it was hard to understand what he said. Hearing was impaired; he was totally deaf in the right ear. He was generally slow; there were twitchings of the extremities, and when he walked he dragged the right foot. He was able to give some information about himself. He said that he had been well until his mother died ten years before, when he had a "shock" and was sick in bed for four days. He stated that he worked in mills and was making $7 a week. He denied having any hostility toward his family, but stated that youngsters teased him and called him "a dirty Irishman." He admitted that he was "nervous" and said that his sister made him so by treating him like a child. He was correctly oriented in all spheres and performed simple mathematical operations correctly. He expressed the idea that his brothers and sisters wanted to kill him so that he would be out of the way. He denied having any interest in girls or having had any sexual relations.

Physical examination gave essentially negative results. A blood count on admission showed a moderate secondary anemia, with 3,776,000 red cells and 80 per cent hemoglobin. The spinal fluid contained 3 cells, and the colloidal gold

curve had a slight elevation in the middle zone. The Wassermann reaction was negative. Examination of the urine gave negative results.

Course.—After admission to the hospital there was gradual intellectual impairment. The patient became careless in dress and untidy in habits. He became stiff and rigid, with increased difficulty in locomotion due to both spasticity and rigidity of the muscles. Neurologic examination on Oct. 25, 1932 revealed a small, middle-aged man who made a striking appearance on account of a peculiar gait. He walked sideways, with the left shoulder higher than the right and with a marked turning of the head to the right. The face had a tense, and at the same time sardonic, expression. This, together with posturing of the head, gave him a grotesque appearance. The gait was crisscross, and in walking he touched the heel of one foot with the toes of the other. It was difficult for him to walk on account of the extreme hypertonicity of the muscles. The cranial nerves were normal, except for bilateral deafness. The right pupil was sluggish in reaction to light. The knee jerks were active and equal. There was ankle clonus on the right and suggested ankle clonus on the left. The big toe on the right was in spontaneous extension, but stimulation of plantar skin on the right resulted in flexion. The abdominal and cremasteric reflexes were present. The patient could utter only a few words, which had to be interpreted by an attendant who knew him well. In this respect there had been definite impairment since admission five years previously.

Subsequent neurologic examinations showed that the associative movements were decreased. The most striking feature was waves of hypertonicity with alternate periods of relaxation, so that at one time he appeared extremely spastic and showed a Babinski sign, while at other times he was relaxed and the reflexes were normal. Under emotional stimulation, when he was suddenly told to run fast he did it quickly and gracefully, but he returned quickly to his grotesque, stiff posture. In addition, there was generalized psychomotor retardation. He could be communicated with by writing only; by this he showed that he was fairly well oriented and clear.

On psychometric examination he performed poorly with the Binet test, but well with the performance test, although the time was decreased. He did unusually well in the interpretation of pictures, and the psychologists thought that he probably had had originally a basal intelligence quotient around 100.

It was also noticed, in 1932, that he had extreme difficulty in manipulating food. It would take him a long time—sometimes as long as two hours—to eat a meal, and there was extreme retardation in carrying the spoon to his mouth. He also had difficulty in swallowing. All these symptoms increased markedly, resulting finally in emaciation.

A roentgenogram of the skull, taken on Nov. 1, 1932, showed masses of dense material in the vicinity of and above the choroid plexus (fig. 1). The significance of these deposits of calcium could not be determined by the roentgenologist. Pneumo-encephalography, six months later, showed slight atrophy of the frontal lobes, some internal hydrocephalus and dilatation of the fourth ventricle. One hundred and fifteen cubic centimeters of fluid was withdrawn and replaced by an equal amount of air.

During 1933, the patient showed a great deal of habit deterioration. He spilled food over himself; he was not tidy in personal habits and refused to do simple work around the ward. Articulation became progressively more impaired, and it was extremely difficult for him to walk even a few steps. The whole

body appeared to be contorted by a powerful spasm. Feeding became a problem, and in October it was noted that there was marked atrophy of the muscles of the body. It was thought that perhaps the case was one of a myotonia atrophica, and a glycine diet with 100 Gm. of gelatin daily was given. At that time the blood creatinine was 2.2 mg. per hundred cubic centimeters. Examination of the spinal fluid never revealed anything abnormal, except that one specimen, taken on March 6, showed total protein of 38 mg. On November 9 there were generalized convulsions involving alternately various groups of muscles. At other times there were twitching of all the muscles of the body, such as one finds in generalized cortical irritation, and the whole body appeared to be fibrillating. The muscles involved were those of the head, eyes, neck, shoulders and extremities.

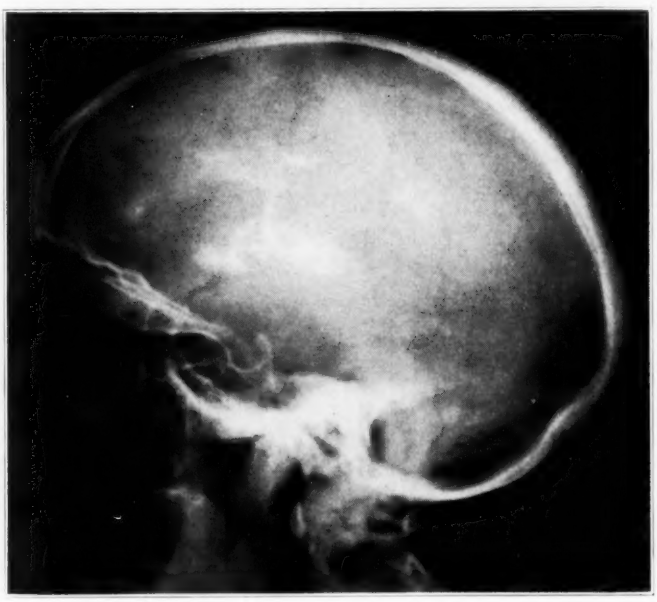

Fig. 1.—Roentgenogram of the skull, showing shadows in the region of the basal ganglia and scattered shadows in other parts of the brain.

The neck was bent backward, but there was no rigidity. The spinal fluid did not seem to be under pressure, and withdrawing some did not stop the convulsions. The spinal fluid calcium was 9.4 mg. per hundred cubic centimeters. The intravenous administration of magnesium sulphate had no effect. The convulsions lasted for six hours; after this the patient became extremely dehydrated and emaciated. On November 16 he died, without having regained consciousness since November 9, when the convulsions began.

Necropsy.—This was performed one and a half hours after death. There was extreme emaciation, with moderate symmetrical wasting of all the skeletal muscles. No gross lesions were noted in the lungs. The heart weighed 140 Gm., the myocardium was pale, but without other apparent change, and the valves of the heart were of normal appearance. No marked degree of sclerosis was

present in the aorta, coronary arteries or peripheral arteries. The liver, spleen and kidneys were all below normal weight, but without conspicuous lesions. All the other organs of the trunk were examined, and no significant lesions were noted. No lesions of significance were observed in microscopic sections of these organs. Sections of striated muscle exhibited atrophic changes in the muscle bundles and nuclei, with increase of fibrous tissue.

The skull and its bony sinuses appeared normal. The sella turcica was of average size and contour. The dura was of normal appearance and was under normal tension. The leptomeninges were slightly opaque over the frontal region, but without signs of inflammatory reaction. The walls of the arteries at the base and over the surface of the brain were thin and without signs of advanced arteriosclerosis. The entire brain was symmetrically atrophic, exhibited no external focal lesions and weighed 1,020 Gm. Sections of the brain were removed for fixation in alcohol; the remainder of the organ was hardened in solution of formaldehyde.

On sectioning the fixed brain the edge of the knife met with resistance and definite grating beneath the cortex. In the white substance of both frontal lobes were accumulations of hard sandlike material, more than 1 cm. in diameter (fig. 2). In the caudate and lenticular nuclei the internal capsule and thalamus were stony-hard, discrete concretions measuring up to 5 by 8 mm. across (fig. 3). At the bases of some of the deeper sulci were layers of sandlike deposits which followed the curve of the deeper cortical layers, with involvement of both cortical and subcortical tissues. Over all the cut surfaces of the cerebral and cerebellar hemispheres and the pons were numerous hard, translucent arteries extending above the surfaces like the cut ends of wire. The dentate nucleus, the white substance and the granular layer of the cerebellum contained sandlike deposits similar in appearance to those in the cerebral hemispheres. The pons appeared smaller than normal and contained vascular lesions resembling those already mentioned. The medulla and spinal cord were small, but without lesions of the type seen in other parts of the central nervous system. The central canal of the cord was widened in the lower cervical and thoracic regions.

Methods: Frozen sections from various parts of the cerebral hemispheres and spinal cord were prepared and stained by the following methods: scarlet red and hematoxylin; nile blue sulphate, and osmic acid stains for lipoids; the silver nitrate method of Klotz and of von Kossa, and alizarin stains for lime salts; amyloid stains; Globus' modification of Cajal's gold sublimate method, and Penfield's stain for microglia and oligodendroglia. Blocks from many areas of the cerebrum, cerebellum, pons, medulla, choroid plexus and spinal cord were embedded in pyroxylin (celloidin) and in paraffin, and sections were stained by the following methods: hematoxylin and eosin, cresylecht violet, Weigert's elastic tissue stain, Weil's myelin stain, Weil's glia stain, Bielschowsky's stain, Holzer's stain, Mayer's amyloid stain, ammonium sulphide and potassium ferricyanide (Turnbull's blue), potassium ferrocyanide and hydrochloric acid (berlin blue), alizarin and the silver nitrate method of Klotz and von Kossa. Decalcification of tissue from the basal ganglia was necessary, but most of the sections were prepared without this procedure. Bubbles of gas were produced when the deposits were brought in contact with hydrochloric acid.

Operations: In all the sections studied the cortical architecture over the convexity of the cerebrum and cerebellum appeared normal. In the depths of the deeper sulci the walls of the capillaries and precapillaries were filled with

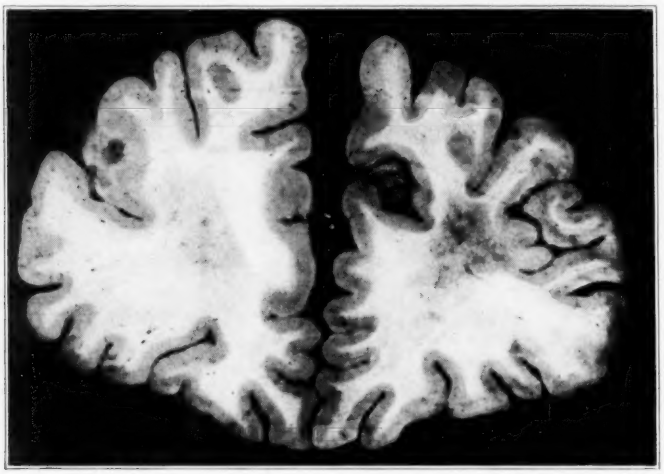

Fig. 2.—Section through the frontal region of the brain, showing sandlike deposits in the white substance of both cerebral hemispheres.

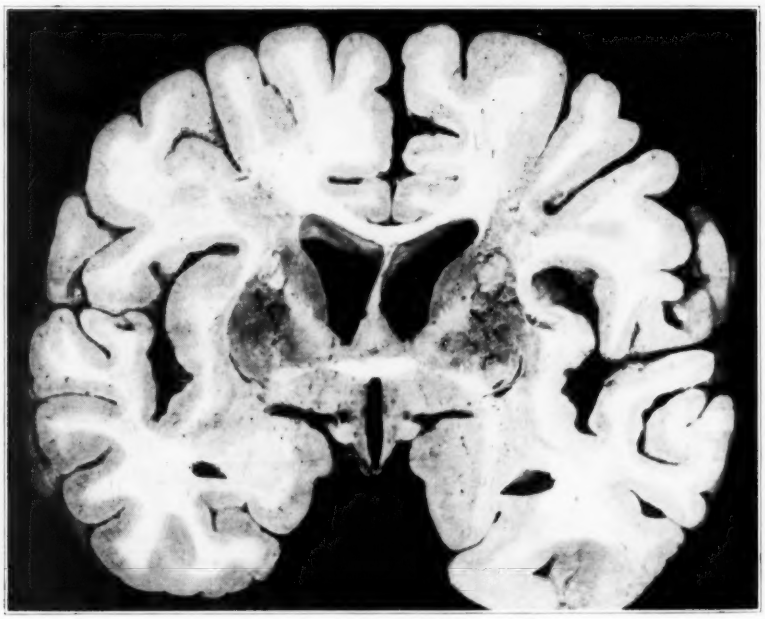

Fig. 3.—Section of the brain, showing calcareous concretions in the basal ganglia and sandlike depositis in the white substance and in the depths of sulci.

droplets of material stained deeply with hematoxylin and cresylecht violet (fig. 4). At the edge of the lesions these varied in size from extremely minute droplets to droplets a size larger than a glia nucleus along the capillaries. Nearer the center of the lesion they became more numerous and tended to form a complete sheath about the vessel. Associated with these capillary deposits in the same region was a smaller number of mulberry-shaped masses, which appeared to be formed by the fusions of several smaller droplets (fig. 5). In the same area were larger bodies, some of which were the size of a large nerve cell, of variable shape (often with a concentric ringlike appearance) and variable staining reactions; these were present near vessels showing deposits. These three types appeared identical with the degeneration bodies described by Hurst,[8] Ostertag[11]

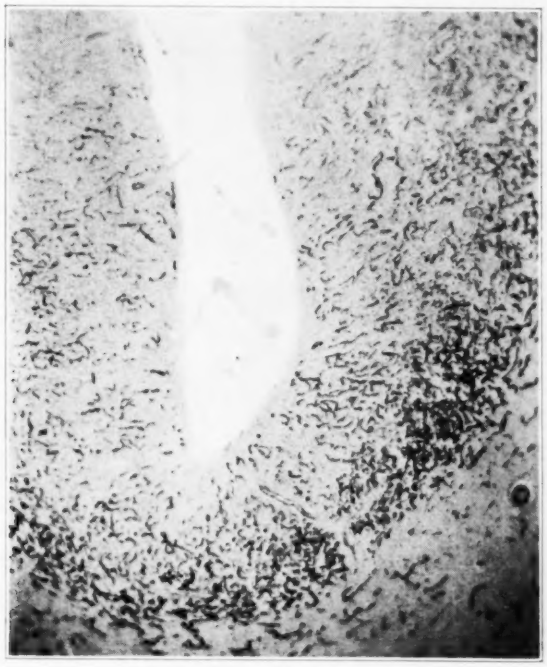

Fig. 4.—Section through a cortical lesion at the bottom of a sulcus in the right temporal lobe. The reaction is most intense in the deeper cortical layers. Hematoxylin-eosin stain; magnification, × 30.

and others. The cortical lesions usually began in the second layer and extended through into the subcortical areas below. Adjacent to these areas the adventitial cells of the capillaries were packed with droplets of lipoid material. The nerve cells over the convexities of the gyri showed only minor variations from their normal appearance; within the sulci were changes which were progressively more severe toward the deeper portions, with loss of Nissl substance, swelling, lipoid inclusions and inclusions stained black with silver salts (fig. 6). Few or no nerve cells were present at the sites of maximal reaction in proportion to the severity of the capillary lesions.

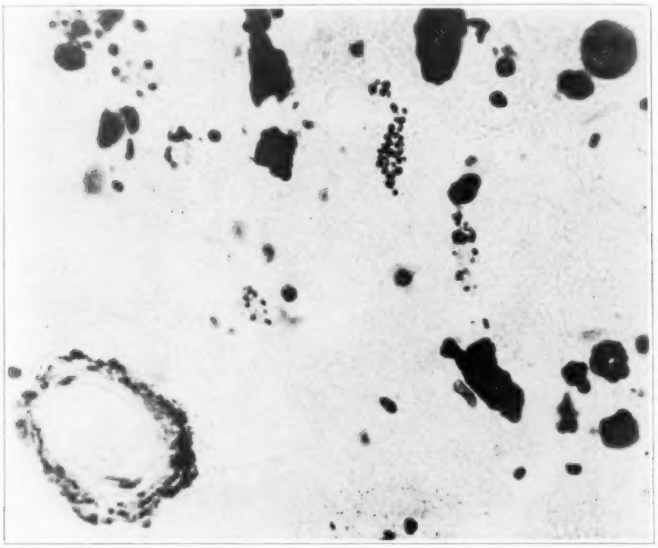

Fig. 5.—Degeneration bodies in the wall of an artery and along capillaries, consisting of minute globules varying in size up to that of a glial nucleus; larger mulberry-shaped masses apparently formed by the fusion of several small droplets, and one spherical body. Cresylecht violet stain; magnification, × 400.

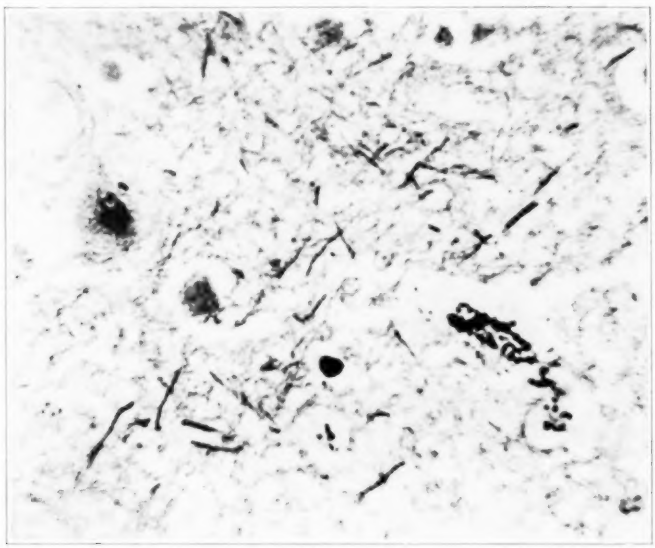

Fig. 6.—Nerve cell from the left parietal cortex, containing a deposit of argentophilic materials, and a capillary with black-stained droplets in its wall. Bielschowsky stain; magnification, × 400.

The subcortical areas examined showed foci of capillary lesions similar to those in the cortex. The extravascular deposits there were relatively more numerous than in the cortex. Most of the arteries showed infiltration of the adventitia by homogeneous material which was similar in appearance to that in the capillary walls and which in many instances extended to the media, filled the Virchow-Robin spaces and encased the artery in a complete sheath.

The process in the basal ganglia was of the same type but much more intense and advanced. Few capillaries or smaller arteries remained open for the circulation of blood, and few cells remained in the vicinity of the more advanced lesions.

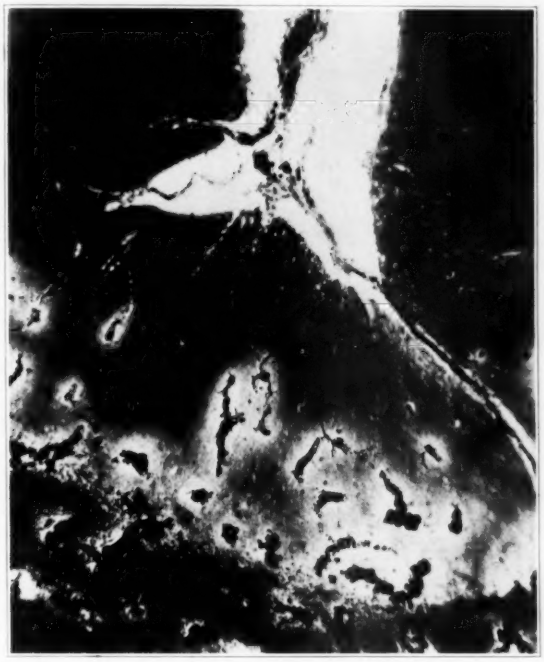

Fig. 7.—Capillary deposits in the cerebellar cortex. The lesion is most intense in the granular layer at the depths of sulci; marked glial reaction is absent. Weil glia stain; magnification, × 100.

Similar lesions were present in the capillaries and arteries of the cortex, white substance and dentate nucleus of the cerebellum, and in the pons, where the process was less advanced and was localized in the central portion (fig. 7).

The veins throughout the brain appeared free from the lesions present in the arteries and capillaries, although in the zones of greatest reaction some of the smaller veins may well have been involved and the process may not have been recognizable on account of the extensive reaction. In addition to the loss of cellular elements, there was loss of myelin in the areas of the subcortical capillary lesions.

The choroid plexus was small, with no conspicuous change in structure or in its blood vessels. It appeared pale, and in sections the blood vessels seemed less abundant than normal.

No lesions were observed in the meninges and meningeal vessels other than a few corpora amylacea in the deeper portions of some sulci over the cerebrum and cerebellum.

Evidence of vascular disease was absent in the lower levels of the medulla and in the spinal cord. There was some gliosis about the central canal of the cord, with widening of the canal in the cervical and thoracic portions.

A concretion from the lenticular nucleus was divided into two portions; one portion was examined chemically, and the other was decalcified for microscopic study. After desiccation the former portion contained 95.3 per cent calcium salts, with a small amount of iron. Examination of the latter portion showed

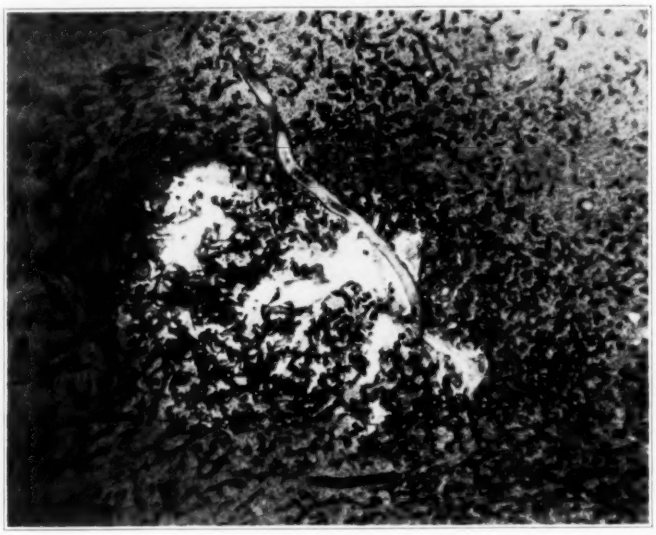

Fig. 8.—Section through decalcified concretion from the basal ganglia, showing capillary deposits and one small calcified artery crossing the center of the section. A portion of this concretion was examined chemically and the presence of a large amount of calcium salts demonstrated. Hematoxylin-eosin stain; magnification, × 21.

that it was composed of homogeneous capillary deposits, with degeneration bodies similar to those described in association with the lesions already described (fig. 8). Thus it is evident that the degeneration bodies in this region must be the seat of true calcification associated with small quantities of iron.

The Turnbull blue and berlin blue methods for the detection of iron showed positive reactions in all the capillary deposits examined. Gans[16] stated that normal reactions for iron are not obtained if the material has been kept in solution of formaldehyde longer than three days. Part of this material had remained in solution of formaldehyde for several weeks before examination; therefore,

16. Gans, A.: Iron in Brain, Brain **46**:128 (May) 1923.

it may be assumed that the reaction obtained was due not to the readily soluble physiologic iron but to some much less soluble substance.

The older stains for the demonstration of calcium are the hematoxylin and silver nitrate stains. Hematoxylin gave intense staining of all the deposits both before and after decalcification. Cameron [17] stated that hemotoxylin has no direct relation to the presence of calcium salts, but is dependent on the essential ground substance and the presence of certain heavy metals. The silver nitrate method of Klotz and of von Kossa gave excellent demonstrations of some of the deposits in more advanced lesions. Most of the larger degeneration bodies in all the advanced lesions examined gave positive reactions before decalcification. These reactions are dependent on the presence of phosphates and carbonates and are not due to the action of the silver on calcium. With positive stains it

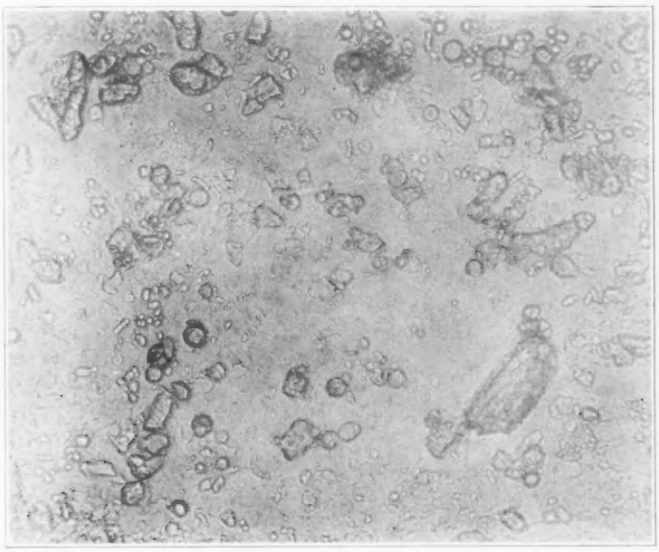

Fig. 9.—Section through a deposit in basal ganglia, not decalcified or stained, showing irregular crystals, droplets with apparent tendency to fusion and spherules with a concentric appearance. The resemblance of the deposit to that of inorganic calcium salts precipitated in a colloidal medium may be noted. Magnification, × 100.

may be assumed that phosphates and carbonates are present, and since the presence of calcium has been demonstrated in a similar lesion it seems reasonable to assume that the deposits stained with these methods indicate the sites of deposition of calcium. In addition to the degeneration bodies, the deposits in the adventitia of many arteries gave positive reactions with these methods.

Cameron [17] showed that derivatives of madder, which were first introduced by Grandis and Mainini,[18] are almost specific for calcium in vitro and in vivo. Alizarin stained many of the deposits in a selective manner, analogous to that

17. Cameron, G. R.: Staining of Calcium, J. Path. & Bact. **33**:929, 1930.
18. Grandis, V., and Mainini, C.: Arch. ital. de biol. **34**:73, 1900.

obtained with silver nitrate methods. There was some gradation from the pink of the pure calcium reaction to the purple or bluish red of deposits containing iron in addition to or without lime salts.

Unstained sections cut through the sites of deposition, without previous decalcification, showed distinctly the nature of the deposit (fig. 9). The spherules and the clumps of granules with a marked tendency to fusion resembled closely the deposit of calcium carbonate precipitated in colloidal solutions, first shown by Rainey [19] and later by Watt [20] and others.

The methods just described demonstrated deposits of iron, without the presence of calcium (pseudocalcification), in the less extensive lesions of the cerebral cortex and pons. The presence of iron was proved by typical staining reactions and by chemical methods. True calcification was demonstrated in the basal ganglia, the cerebral cortex and white substance, the cerebellar cortex and white substance, the dentate nucleus and the pons. The presence of calcium was assumed on the basis of the following observations: (1) the resemblance of the unstained deposits in certain areas to that of calcium salts precipitated in a colloidal medium; (2) the occurrence of decalcification under appropriate treatment, with resultant altered staining reactions in the organic ground substance; (3) the characteristic staining reactions of silver nitrate and of alizarin, and (4) chemical evidence of the presence of a high percentage of calcium in a typical lesion.

In the case described there was no evidence of neoplastic activity; there were no living cells included anywhere in the masses, such as are seen in developing bone; the deposits were not associated with any one type of cell, but were present in the walls of blood vessels, in tissues adjacent to the blood vessels and occasionally in nerve cells; there was no definite cell membrane surrounding the masses to which their origin could in any way be ascribed; and the masses of calcium were not encapsulated or ensheathed as though there was any appreciable tissue reaction to them. Cellular activity, therefore, would seem to be eliminated as an active agent in the process, and the manner of deposition of calcium salts was assumed to be that of precipitation. This may be in the form of calcium carbonate or phosphate originally,[21] or as calcium soaps first,[22] with gradual conversion into the carbonate and phosphate.

COMMENT

The case described is that of a man who had convulsions in youth, followed by gradual intellectual impairment and the appearance of marked extrapyramidal signs with extreme hypertonicity of voluntary muscles. The pathologic picture was one of extensive calcification of the finer cerebral vessels, so gross that its presence was clearly seen in roentgenograms. A review of the literature shows that the clinical pictures in such cases have only one thing in common—the presence of areas of calcification in the brain. Some patients with gross calci-

19. Rainey, G.: Brit. & Foreign Med.-Chir. Rev. **40**:343, 1857.

20. Watt, J. C.: Deposition of Calcium Salts in Areas of Calcification, Arch. Surg. **15**:89 (July) 1927.

21. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 497.

22. Klotz, O.: Staining Reactions Suggesting the Presence of Calcium Soaps in Tissues, J. Exper. Med. **7**:633, 1905; **8**:322, 1906.

fication of the brain may show no psychotic signs. Others show only neurologic signs pointing to a focal involvement of the brain, which, coupled with the roentgen findings, suggest a tumor.

The cases reported show a certain variability in the clinical picture, with two findings common to all: the insidious development of the lesion, with or without psychic or neurologic evidence, and deposits demonstrable by the roentgen rays. There is, however, a group of cases which present a clinical syndrome characterized by: (1) a suggestion of familial incidence, (2) convulsive phenomena and (3) gradual mental impairment, with or without the development of a psychosis. The case presented probably belongs in this group. There is a suggestion that one of the sisters is showing the same syndrome as the patient.

The calcification of the finer cerebral blood vessels is not proportional in extent to the clinical syndromes reported. In all the cases described there was selective involvement of the capillaries, arterioles and smaller arteries of the brain. The veins were relatively unaffected. In all the calcified and noncalcified lesions an albuminoid matrix with a basophilic staining reaction was present. According to Mallory,[12] this material has a tendency to undergo calcification. The presence of pathologic iron without calcium in the less advanced lesions and the presence of iron with calcium in the older deposits suggest that deposition of iron preceded calcification. Ehrlich [23] suggested that pathologic iron in certain tissues may act as a mordant for subsequent deposition of calcium.

The etiology of the condition is obscure. Inflammatory, neoplastic and cellular origins appear to be eliminated; no lesions were present anywhere in the body which might suggest a toxic etiology. The earliest lesions were colloid degenerations in the adventitial cells of the finer cerebral blood vessels, with little or no reaction on the part of the surrounding tissues. Deposits of calcium of this type seem to be dependent on local conditions [24] rather than on general disturbances of calcium metabolism. Apparently such calcifications are not caused, although they may be modified,[25] by the state or amount of calcium in the circulating blood.

SUMMARY AND CONCLUSIONS

1. A case of extensive calcification of the finer cerebral blood vessels in a man, aged 32, is reported, which was characterized clinically by gradual intellectual impairment, convulsions and marked extrapyramidal signs, with a dystonia-like picture.

2. The lesion was one of degenerative changes in the finer cerebral blood vessels, with the formation of an albuminoid matrix containing iron and the subsequent deposition of calcium salts by precipitation.

3. The clinical picture in cases of extensive calcification of the brain, as reviewed in the literature, is variable; the one common finding is the presence of deposits demonstrable in encephalograms.

4. Although the clinical picture is variable, there is a group of cases, including the one described here, which is characterized by: (*a*) probable familial

23. Ehrlich, S.: Centralbl. f. Allg. Path. u. path. Anat. **17**:177, 1906.

24. Barr, D. P.: Pathological Calcification, Physiol. Rev. **12**:593 (Oct.) 1932.

25. Menkin, V.: Calcification of Tubercles by Administration of Calcium Chloride, Proc. Soc. Exper. Biol. & Med. **28**:1001 (June) 1931.

incidence; (*b*) early beginning of intellectual impairment; (*c*) convulsions; (*d*) various neurologic signs, depending on the location of the lesions, and (*e*) extensive calcification of the finer cerebral blood vessels.

5. There is no direct evidence of general disturbance of the calcium metabolism. Further investigation along this line is indicated. The etiology is unknown.

DISCUSSION

Dr. C. A. McDonald: I do not know much about calcification of the brain, but I think that it is an extensive process. Recently I had a patient, aged 16, who showed calcification. I have brought some roentgenograms showing another type of calcification—so-called brain stones. I congratulate the reader on his well worked-up report. These roentgenograms are those of a young man who had some fits which were finally diagnosed as jacksonian convulsions. He was operated on and died.

Dr. William Hughes: It is of interest that the patient had convulsive states. As I understand it, calcification occurs in areas in which there is little oxygen, e. g., in the center of tubercles in the lungs. Lack of oxygen in certain areas in the brain has been considered one of the chief factors in the production of convulsive states.

Dr. H. H. Merritt: This case is unusual; so far as I know, there is no case in the literature exactly like it. I know of a family in which areas of calcification in the basal ganglia were shown by roentgenograms. The spinal fluid calcium was very high in the case presented by Dr. Kasanin and Dr. Crank. I wish to ask Dr. Kasanin whether he estimated the blood calcium and whether or not deposits of calcium were found in the viscera.

Dr. J. Kasanin: I did not estimate the blood calcium. I have no idea what the origin of these deposits of calcium is. There were calcified areas in, around and outside the blood vessels. Perhaps the condition can be explained by the smallness and inefficiency of the choroid plexus.

SPECIAL ARTICLE

CLAUDE BERNARD

1813–1878

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AND
JEAN SAUCIER, M.D.
MONTREAL, CANADA

Claude Bernard, who was destined to become the father of experimental medicine, was born in the little village of St. Julien in the department of the Rhône on July 12, 1813. Not a great deal is known of his early years, but he attended the Jesuit College in the nearby town of Villefranche and evidently showed promise, as he was later sent to Lyons to continue his studies. Instead of completing these, however, he entered the shop of a pharmacist in which he acted as dispenser. The work neither impressed nor appealed to him, and indeed his main attention was directed to the theater, which he frequented as often as possible. This led him to the writing of a play, "La rose du Rhône," which was produced with some success. Encouraged by the result, he turned his attention to the composition of a historical drama and, on its completion, set out for Paris with the play and with a letter of introduction to Saint-Marc Girardin, an eminent critic and professor at the Sorbonne.

Of the two, the letter was of more value to him and to posterity than the play, as the latter was never produced but was published only after the author's death. Girardin recognized the ability of the youth as a dramatist but dissuaded him from cultivating this as a vocation. Instead he advised him to take up some study by which he might more easily earn his bread and, in view of Bernard's apprenticeship to the pharmacist, suggested that he study medicine. The young man followed this advice and devoted himself assiduously to his work. He was particularly interested in anatomy and physiology and, even in his student days, he and a friend opened a laboratory by means of which they hoped to earn a little money and to carry on their researches. The venture was not successful, however, and soon had to be abandoned. While his interest in his practical studies was sustained, he was not regarded as an outstanding student in the classroom. In his fifth year he was appointed "intern" to the gruff Magendie, who was at that time the leading physiologist in France and a man of far-reaching influence. Magendie soon recognized the value of his young assistant, his applica-

tion and his manual dexterity and appointed him *préparateur* in his laboratory in the *Collège de France;* thus, in 1841, did Bernard's real career begin.

At this time physiology was just beginning to free itself from the scholasticism of the past. The influence of vitalism, which denied the efficacy of the experimental method in the study of the phenomena of living things, was keenly felt, and perhaps most so in France. The ideas of Cuvier, an ardent supporter of vitalistic views, and of Bichat, the brilliant investigator who had died at the early age of 31, were dominant in the physiologic tradition of that country. Even Magendie felt this influence and accepted the popular division of living phenomena into two groups: those which could be approached experimentally and those which, because of their native vitalism, could not. Into a study of the first class he threw himself with great vigor, but most of his effort was given to the experiment itself and little to its reasoned preparation and to a critical consideration of its results.

Bernard, on the other hand, in the evolution of his work did not recognize this division but approached all problems in which he was interested in exactly the same way. "There is but one expression of life," he said, "one physiology embracing all things." Furthermore, his experiments were never haphazard but were the preconceived and carefully planned tests by which he meant to prove or disprove some idea which he had evolved. Renan, who was elected to the seat in the Academy of France which was vacated on Bernard's death, and who, according to custom, delivered a eulogy of the man whom he was succeeding, remarked on the complementary natures of Magendie and Bernard. He stated that had these two not been thrown together as they were Magendie would not have attained the eminent place which he did and Bernard would, perhaps, not have been able to surmount the material difficulties which would have confronted him in his life of research.

In 1843 Bernard's first work was published under the title "Recherches anatomiques et physiologiques sur la corde du tympan, pour servir à l'histoire de l'hémiplégie faciale." A few months later the thesis for his doctorate, "Du sucre gastrique et de son rôle dans la nutrition," appeared. These titles are of particular interest because, built up on them, were Bernard's two greatest contributions to physiology.

Bernard early interested himself in the problems of nutrition and digestion. In 1849 he published the results of some experiments on the physiology of the pancreas. At the time this organ was poorly understood, but he succeeded in showing that it played an important part in the digestion of protein, fat and carbohydrate. For this work he was awarded the Prize of Experimental Physiology by the *Académie des*

Sciences, and through it he became recognized as an investigator of note. He next decided to follow the steps in the digestion and metabolism of each of the three types of food; he began with the carbohydrates because he had carried out investigations of these before and because he was interested in diabetes mellitus. He never passed beyond these, however, as they involved him in years of work and led to his greatest single discovery, the glycogenic function of the liver.

CLAUDE BERNARD

1813–1878

It is of interest to read the description of the steps in this piece of work as they are recorded in Sir Michael Foster's biography of Bernard. He had known before that carbohydrates are changed into dextrose before being absorbed and reasoned that if he followed the dextrose to the point where it disappears he could then postulate that diabetes consists of a failure of that region to dispose of the sugar. He soon found that there was dextrose in the hepatic vein leaving the liver, but in order to determine whether it was the same as that which

had been ingested he fed the animal on a carbohydrate-free diet. But sugar was still present in the hepatic vein, and the same condition existed even if the animal was starved. So, he concluded, the liver manufactures dextrose, and this is given to the blood as an internal secretion. He next washed the liver free from albumin and sugar and found that after an interval fresh washings contained sugar. If the liver was heated to a certain temperature sugar could no longer be obtained from it, but if some fresh liver was added to the preparation the dextrose again appeared. To the substance from which the dextrose was produced he gave the name glycogen.

In the course of these studies he decided to investigate the action of the nervous system on this function and believed that the vagus was the nerve to be studied first. Remembering an earlier experiment in which he had irritated the fifth nerves by making a puncture in the region of their nuclei, he decided to carry out comparable experiments on the vagus and so made his famous lesion in the floor of the fourth ventricle. Glycosuria followed the procedure. It is apparent, therefore, that this was not a chance finding but was the result of a carefully planned and logically considered research. Bernard soon found, however, that the vagi were not the nerves through which this result was brought about.

This, all too briefly, is a description of Bernard's epoch-making discovery. In one series of experiments he disproved the prevailing belief that animal life, in contrast to plant life, could only break down and could not synthesize; he proved that vital phenomena could be approached experimentally and could be shown by this means to conform to laws; he applied physiologic methods to the study of clinical disease; he originated the idea of internal secretions which pass directly into the blood and attempted to correlate the functions of the bodily organs with the nervous system. Furthermore he himself, from start to finish, had described the various steps concerned in the glycogenic function of the liver; he alone was the father of this concept. In Foster's words "Bernard started the fox, was at the head of the pack through the whole run, and was first in at the death."

Bernard's second great discovery was that of the vasomotor nervous system, but in this he was not so alone. Although he was the first definitely to prove its existence, his results were appreciated by others even before they were by himself. In 1840 Henle had asked the question: Why do sympathetic fibers, apparently motor in nature, go to arteries if these, as supposed, are devoid of muscles? He concluded that the middle coat of the arteries is, at least in part, muscular. In the same year Stilling, arguing on theoretical grounds, proposed that there were involuntary motor nerves which determine the movements of the blood and to these he gave the name vasomotor nerves. But not

until Bernard's work was the clear proof of the existence and action of vasomotor nerves forthcoming.

In an attempt to study animal heat and the effect of the nervous system on it Bernard severed the cervical sympathetic chain in the neck. He chose the sympathetic nerves because these accompanied the arteries and he considered that they were more likely to be concerned in metabolic exchange between the blood vessels and the tissues. He had expected to find a lowering of temperature in the parts supplied by these nerves and was surprised to find the reverse. He found a rise in the temperature of the head and neck on the side of operation, increase in sensibility and dilatation of the arteries. He described all these changes but directed least attention to the arterial dilatation; he maintained then, and for the rest of his life, that the vasodilatation was not alone the cause of the increased temperature but that the latter depended "on actions of two kinds, on a vascular action and on a concomitant chemical action." Shortly afterward, Brown-Séquard (then in America) and a little later, and independently, Bernard himself described the vasoconstriction which followed stimulation of the distal segment of the divided sympathetic.

Six years later, in 1858, Bernard announced that blood issuing from the actively secreting submaxillary gland is not dark like that issuing from an active muscle, but is bright like arterial blood. A month later he reported that this occurred only as a result of stimulating the chorda tympani. On the other hand, if the sympathetic supply to the gland was stimulated, the issuing blood was dark, even more so than usual. Furthermore, the flow in the former case was full and rapid, in the latter scanty and slow. He concluded that the difference in color was due to "mechanical modification brought about in the capillary circulation by the two nerves respectively" and that "the sympathetic nerve is the constrictor nerve of the blood-vessels; the tympanicolingual (chorda tympani) is their dilator."

Of these investigations Foster said: "To Claude Bernard, then, we owe the foundations of our knowledge of the vasomotor system. He made known to us the existence of vasomotor nerves, and he also made known to us that vasomotor nerves are of two kinds, vaso-constrictor and vaso-dilator. These are the two fundamental facts of vasomotor physiology; all else supplied by many others is built up on these."

These, then, were Bernard's two chief pieces of investigation. In addition, he turned his attention to many other problems, and his publications were numerous, filling eighteen volumes. Among the subjects he studied were the gastric juice, the spinal accessory nerve, "recurrent sensibility," inhibition of the heart by stimulation of the vagus and the action of such poisons as curara and carbon monoxide, and he was engaged on the problem of fermentation at the time of his

death. Cannon and Fulton have recently emphasized another of the contributions of Bernard to science, his conception of the "*milieu intérieur*," the internal environment. Briefly, it is that higher forms of life have within themselves a mechanism for maintaining almost absolute constancy of the body fluids. Of this Bernard said that "the nervous system is called upon to regulate the harmony between all these conditions" and Fulton commented that "in this forecast lie the greatest problems of physiology and medicine of the immediate future," the regulatory action of the autonomic nervous system.

In the first lecture which Bernard delivered to students he introduced his subject with the words, "Scientific medicine, which I am supposed to teach you, does not exist." How different was the state of affairs at his death and how great a part he played in that change. In his work, in his scientific achievements and in his writings he was always the advocate of the application of the methods of experimental physiology to the study of medicine. He refused to accept the empiricism of the past but preached the doctrine of determinism, the conformity to law of cause and effect. In 1865 he published his "Introduction to the Study of Experimental Medicine," which has been translated into English and which contains the master's philosophy and creed.

His eminence was recognized and honors were heaped on him both before and after his death. For several years he deputized for Magendie and on the latter's death, in 1855, he was appointed professor at the *Collège de France*. He was elected to the Academy of Medicine and Surgery in succession to the great surgeon Roux. In 1864 he was summoned to the presence of the Emperor Louis Napoleon, who was so impressed by the scientist that he established two laboratories for him, one at the Sorbonne and the other at the *Muséum d'Histoire Naturelle* in connection with a chair of general physiology. In 1868 he was admitted to the *Académie Française*, the highest honor which could come to him. Shortly before the revolution the Emperor made him a member of the Senate, but he never took his seat.

His family life, however, was more unfortunate. His wife and two daughters left him, and one of his daughters spent much of her means in founding hospitals for dogs and cats in an effort to atone for the sins of her father. On his death he was universally mourned and was given a state funeral, the first man of science or letters to be so honored by France. Statues were later erected to his memory in the *Collège de France* and in the Faculty of Medicine and Science at Lyons.

Bernard died on Feb. 10, 1878, an Immortal of France and an Immortal of Science.[1]

1. In the preparation of this biography, the following publications have been freely quoted: "Claude Bernard" by Michael Foster (Longmans, Green & Co., New York, 1899); "Claude Bernard" by J. L. Faure (G. Crés et Cie, Paris, 1925); "L'Oeuvre de Claude Bernard" (J. B. Baillère, Paris, 1881).

Abstracts from Current Literature

THE PROBLEM OF SYSTEM DISEASE. WALTHER SPIELMEYER, Jahrb. f. Psychiat. u. Neurol. **51**:256, 1934.

The problem of system disease, according to Spielmeyer, cannot be discussed without a clear understanding of the general problem of degenerative diseases of the nervous system. Spielmeyer believes that the designation "degenerative process" in nervous diseases should be applied only to conditions in which there occurs a regressive disintegration of functioning nerve parenchyma without evidences of definite types of products of degeneration by which the peculiar type of regressive change can be recognized. The outstanding feature of a degenerative process, in this sense, must be its primary character; i. e., it must not be associated with inflammation nor must it be due to circulatory disturbances, and the disintegration of the nerve parenchyma must exist without any recognizable disturbance of metabolism. The failure to adhere strictly to these criteria, and at times even the inability to determine their existence with certainty, has led to the loose and not infrequently wholly unwarranted application of the designation "degenerative process" to conditions which were anything but degenerative in the sense of a system disease.

The determination of the existence of a primary degeneration of the nervous system presents two unusual difficulties: (1) the extraordinary chronicity of most of the diseases belonging to this group, and (2) the absence in most instances of definite evidences of a primary type of disintegration of nerve parenchyma. These two difficulties, though encountered in almost every disease of this kind, are most striking in cases of amyotrophic lateral sclerosis and in other conditions in which degeneration of the long tracts is a prominent feature. The first difficulty could be overcome readily if as much were known about primary regressive diseases of the fiber tracts as about wallerian degeneration. In the present state of knowledge the picture of recent manifestations of disintegration of the pyramidal tracts in cases of amyotrophic lateral sclerosis cannot be definitely distinguished morphologically from that of secondary degeneration. In order to understand the nature of system diseases characterized by lesions of the pyramidal tract, it will be necessary to determine whether the essential anatomic changes and the clinical features depend on a primary disease of the tract or tracts involved or whether they are due to some demonstrable change or to an invisible change anywhere in the course of the affected system. To be able to recognize the peculiar characteristics of primary degeneration of the pyramidal tract it will be necessary to determine the various forms which such degeneration may assume and also what the determinants for their occurrence are, and especially whether a degeneration resembling a wallerian degeneration, in which granular cells are mobilized, may occur in one and the same system alongside a slowly destructive lesion with elaboration of *Abbau* products in the fixed glia. This may possibly be so, because in definitely degenerative diffuse processes when the course is slow it is usual to find that only the fixed glia is the scavenger for the products of degeneration, whereas when the course is more rapid and the disintegration more intense granular cells are also necessary to remove the products of disintegration.

Although none of the diseases hitherto recognized as system diseases are entirely "elective" in the sense that they invariably affect purely and exclusively one functionally and anatomically uniform system, nevertheless Spielmeyer does not believe that the entire concept of system disease should be abandoned. The fact that a process is diffuse is, by itself, not a serious objection to the concept. Indeed, certain endogenous noxae may have a predilection for definitely uniform anatomophysiologic units and their associated components and at the same time may also affect to a lesser degree other components of the nervous system (amaurotic family idiocy, Friedreich's disease and cerebellar and cerebellomedullary degenerations). There can be no valid objection to designating these diseases as

"system diseases." Conditions, however, are different in diseases like Wilson's disease in which the status spongiosus may also extend to the external capsule, claustrum, white substance of the insula, pallidum and internal capsule—structures that are anatomophysiologically entirely different in nature. Wilson's disease, therefore, cannot be regarded as a system disease. This also applies to diseases like chronic progressive sclerosis of the cerebral hemispheres—the basis for Pelizäus-Merzbacher's disease—in which foci of demyelinization are also found in the dorsal parts of the basal ganglia. Nor can one include among the system diseases a case of Pick's disease of the type recently reported by von Braunmühl, in which the brains of two sisters showed lesions in the caudate nucleus, internal capsule and globus pallidus. While, therefore, it is true that in all these diseases the pathologic process has a more or less typical site of localization, it is not limited to a uniform anatomophysiologic neural unit or units. This, however, is not the case with amyotrophic lateral sclerosis and its allied spinal muscular atrophy. In this connection, however, Spielmeyer points out that those who do not accept the existence of system diseases may have some basis for their opinion, because even in such diseases as amyotrophic lateral sclerosis and spinal muscular atrophy there may be found alongside the principal lesions in definite tracts and nuclei also lesions in other fiber tracts, and diffuse lesions are not at all uncommon.

A critical study of this problem also reveals that a less radical view of system diseases adds still greater difficulties in the attempt to delimit the concept, as well as in the attempt to find an adequate explanation as to the nature of the diseases usually included among system diseases. Nor is the concept clarified by employing the term "endogenous" in connection with degenerations, for although this term does not carry with it the implication that these degenerations are familial or hereditary, nevertheless many of these diseases are regarded as heredodegenerative. While it is true that such diseases as Huntington's chorea, Friedreich's disease, amaurotic family idiocy, Wilson's disease and even Pick's disease are hereditary, it must also be remembered that there exist many degenerative diseases which are classified as heredodegenerative diseases although their hereditary features still remain to be proved. At any rate, the hereditary nature of a disease cannot be determined anatomically. Unfortunately, there is no such thing as an anatomy of heredodegenerations, even though Schaffer and his school insisted that there is. Schaffer's attempts to differentiate these conditions by attaching to them variously the designations "ectodermogenetic," "endogenous," "ectodermatotropic" and "exogenous" does not help matters. In the absence of precise knowledge as to the etiology of these diseases such classifications are not well founded, and surely anatomically such differentiations are impossible. Schaffer still speaks of "germinal plate," "segment" and "system selection" as the anatomic triad of the heredodegenerations. That this view is not tenable is obvious when one bears in mind that the anatomic picture of toxic system diseases of the nervous system may appear indistinguishable from that of the heredodegenerations.

On the other hand, in an exquisitely familial disease like Wilson's disease the ectoderm is involved as well as the mesoderm. Similarly, with the recognition of amaurotic familial idiocy as a lipoidosis of the Niemann-Pick type, it also became apparent that in this disease, too, there can be no question of a germinal plate, segmental and system selection.

According to Spielmeyer, the most important phase of the entire problem is the question of the etiology of a degenerative process and whether it can be included among the hereditary diseases—in the final analysis it is the study of the causation of the disease. For this it will be necessary to take into consideration clinical experience as well as the hereditary factors involved in diseases the inheritance of which is still in question. This is best illustrated by such diseases as amyotrophic lateral sclerosis, spinal muscular atrophy, etc., the nature of which is still the subject of lively discussion among clinicians. While van Bogaert and recently Marburg have expressed the opinion that amyotrophic lateral sclerosis is not hereditary, Munch-Petersen found familial cases of this disease which could not be distinguished from the usual picture of amyotrophic lateral sclerosis; the clinical facts in these cases leave no doubt as to the nosologic uniformity of the process.

It must be borne in mind, however, that even though clinical and etiologic investigation may have demonstrated familial and hereditary factors in these diseases, their primary degenerative character has not been definitely established. Everything that is hereditary is not necessarily morphologically and pathogenically degenerative. The nature of Wilson's disease, for example, does not become clear merely from the presence of mesenchymatous components in the histologic picture, and, vice versa, a process which is purely degenerative and even systemic is not therefore necessarily hereditary, for exogenous noxae may produce a similar process.

KESCHNER, New York.

THE VESTIBULAR FUNCTIONS OF THE FRONTAL LOBE WITH THE STRIATE BODY: CEREBRAL AND SUPRATENTORIAL ATAXIA. L. J. J. MUSKENS, Rev. d'oto-neuro-opht. **12**:241 (April) 1934.

Muskens discusses forced movements and postural deviations in the frontal plane under the following subdivisions: physiologic observations of forced movements and other "ataxic" manifestations after a lesion of the striatum and of its influence on locomotion and ocular movements; clinical observations of forced movements in the vertical plane in cases of a lesion of the striatum and in cases of cerebral tumor; forced movements and attitudes in a forward direction in cases of a lesion of the striatum; combined forced attitudes. Finally, he discusses the usefulness of the known facts about forced movements and attitudes and falling tendencies in the frontal and vertical planes in the diagnosis of deeply seated cerebral foci.

There exists in the supravestibular system a collection of pathways and nuclei, so situated in the region of the cerebral trunk (extending from the level of the superior olive to the region of the paleostriatum and neostriatum) that a lesion as small in volume as 1 cc. can influence the correct functioning of these structures. The diagnosis of a lesion of the cerebral trunk is attempted by an exact differentiation of the divers supravestibular symptoms. The idea of the French school of alternate paralysis furnishes material for comparison in the diagnosis of a unilateral lesion. Fixed landmarks in the region situated in front of the nucleus of the patheticus nerve are lacking, because notions of the functioning of the oculomotor nuclei, situated in an anteroposterior plane, are still confused; because the importance of the red nucleus, the body of Luys and the black substance is unknown, and because, as regards the thalamus, one can utilize up to the present only the ventral nucleus, seat of the relays of all the pathways of sensibility. A more thorough study of the importance of the posterior commissure and the commissural nuclei, the relations of which with the globus pallidus has just been learned, will give orientation here, as will also a study of the central pathways of the tegmentum, all of which probably terminate in the neostriatum, as is suggested by a study of the supravestibular pathways. While up to now it has been necessary to be content, for the region of the posterior quadrigeminate bodies and the pons, with available ideas on the relations of the ribbon of Reil and of the trigeminal nerve as well as of those of the pyramidal tracts, a more exact comprehension has now been gained of the posterior longitudinal bundle, the central pathways of the tegmentum and of the superior cerebellar peduncle, which send their supravestibular fibers from the roof nuclei into the superior segments (i. e., in the gray substance of the thalamus). There are also sufficient indications appearing to prove that in the paleostriatum the supravestibular center for the tendency to fall toward the sound side is situated farther forward and that for conjugate deviation is situated in the lateral portion; there are a sufficient number of clinical cases of foci in the anterior part of the caudate nucleus to permit the location there of the tendency to fall backward. Precise knowledge is still lacking of the nuclei of the neostriatum and of the central gray substance, lesion of which provokes falling forward, but it appears logical, in accord with the results of experimental physiology and clinical experience, to suppose the existence provisorily of centers in the more ventrally located part of the neostriatum.

Examples of incorrect diagnosis and consecutive operation are met with everywhere in the literature, while a better comprehension of supravestibular symptoms

would have led to a justifiable operation or, more often, to abstention from surgical intervention. The statement that increase of intracranial tension can by itself produce supravestibular symptoms should not change this opinion. The existence of neuritis of the acoustic nerve from intracranial hypertension has not been proved, although the possibility of neuritis of the olfactory nerve is not eliminated. Too much value has been accorded to so-called hyperexcitability of the labyrinth consecutive to certain intracerebral morbid processes. There is danger in assuming too easily that certain attitudes of the head are the direct result of a tendency of the patient to maintain the circulation of the cerebrospinal fluid. The diagnosis of systemic diseases of the nerve fibers or of foci of infection will offer certain difficulties, but this will be compensated for by the fact that in the first instance these diseases (usually symmetrical) present especially supravestibular signs, which are more marked when the pathways on both sides are interrupted. It is not by chance that the most typical cases of vertical paralysis of gaze are due to bilateral vascular disturbances. Likewise, the precocious limitation of the gaze in all directions and the tendency to fall toward all sides which are observed in cases of paralysis agitans have been attributed to a diffuse involvement of all the striate formations. The question whether certain supravestibular manifestations depend on excitation or paralysis will arise only in cases of internal hemorrhage and then may be answered only by the concomitant symptoms. On the base of autopsy observations and experimental findings, it is certain that too often an excitation has been assumed when an interruption of continuity or a nuclear lesion was present. There exist a large number of well studied cases of foci in the cerebral trunk, especially those involving the posterior longitudinal bundle, in which the bundle was situated in the midst of an area of softening and which gave rise to no symptoms. On the other hand, observation has shown that in such cases conjugate deviation or *mouvements de manège* were present; a thorough study of serial sections in these cases would no doubt show interruption of the pathway (posterior longitudinal bundle).

Several schematic drawings of sections of the brain stem and numerous references to the literature are included.

DENNIS, San Diego, Calif.

THE SYMPTOMS AND DIAGNOSIS OF EXTRADURAL CYSTS. CHARLES A. ELSBERG, CORNELIUS G. DYKE and EARL D. BREWER, Bull. Neurol. Inst. New York **3**: 395 (March) 1934.

Extradural or intradural cysts causing compression of the spinal cord are rare and have been found by Dyke and Brewer 5 times in a series of 250 cases of tumors of the spinal cord. The article is based on 4 extradural cysts and emphasizes the symptoms and signs, and particularly the changes visible in the roentgenograms, which should make the diagnosis of this condition possible.

CASE 1.—A boy, aged 12 years, had been seen three years previously because of clumsiness of gait and increasing difficulty in walking for six months. At that time the tendon reflexes of the lower extremities were hyperactive, the abdominal and cremasteric reflexes were absent, no sensory disturbances were found, and a diagnosis of multiple sclerosis was made. Motor difficulty steadily progressed; numbness of the lower extremities and, later, incontinence of urine and feces developed. There was no pain at any time. At the time of the second admission he was unable to stand or walk; there was a marked spastic paraplegia, with bilateral patellar and ankle clonus and a bilateral Babinski sign. The upper abdominal reflexes were absent. There was no motor disturbance of the upper extremities and no disturbance of the cranial nerves. Tactile sensation was slightly diminished below the sixth thoracic dermatome; pain and temperature sensation were slightly diminished to a slightly higher level; vibratory sense was lost in both lower extremities and in the anterior iliac spines. Manometric tests showed a complete subarachnoid block. At operation an extradural cyst extending from the sixth to the tenth thoracic vertebra was found and removed; the patient made a slow but progressive recovery.

CASE 2.—A boy, aged 15 years, had been well until three months before admission, when weakness and numbness of the right lower extremity were noted. These gradually spread to involve both lower extremities. There was no pain and no sphincteric disturbance. The gait was spastic, and there were weakness and spasticity of both lower extremities, especially the right, with bilateral suprapatellar, patellar and ankle clonus, and a Babinski sign and foot drop on the right. Tactile, pain and temperature sensations were slightly diminished below the level of the seventh thoracic dermatome. There was impairment of vibratory and muscle joint sensation in the right large toe. Manometric tests showed complete subarachnoid block. Roentgen examination showed that the pedicles of the seventh, eighth and ninth thoracic vertebrae were definitely narrowed and atrophied, especially on the right, and the interpedicular spaces of these vertebrae were much enlarged. Operation revealed a large, thin-walled cyst, extending from the sixth to the ninth thoracic vertebra. Three weeks after operation strength in the lower limbs was very good; spasticity was slight; the tendon reflexes were only moderately hyperactive, and the abdominal and cremasteric reflexes had returned. Sensation was entirely normal.

CASE 3.—A boy, aged 15 years, had noted weakness and stiffness in the left leg nine months before admission. Within a month he could walk only with the aid of a cane. The right leg quickly became affected, and sphincteric difficulties developed. He was then cared for in another city; incomplete spinal block was found, with sensory changes up to the eighth thoracic segment. What was interpreted as an intradural cyst was incised and evacuated, and the patient experienced rapid recovery of strength, sensation and sphincteric control. Two months after operation the symptoms returned with progressive severity. A second operation and evacuation of encysted fluid again resulted in only temporary relief. At the time of admission to the institute the abdominal reflexes were absent; extreme spasticity of both lower limbs was present, with bilateral suprapatellar, patellar and ankle clonus and a Babinski sign. All cutaneous sensibility was lost up to the ninth thoracic dermatome and was diminished to the seventh. Vibratory and muscle joint sense were lost in both lower extremities. Roentgenograms showed that the pedicles of the fourth to the ninth thoracic vertebra were narrowed and the interpedicular spaces considerably enlarged. Manometric tests showed a complete subarachnoid block. Operation revealed a thin-walled cyst, 12 cm. long and from 4 to 5 cm. wide, which was removed.

CASE 4.—A girl, aged 16 years, was not seen by the authors but a report of the case is included because of a basic similarity to the other cases as to onset and progression of symptoms during two years and the resulting spastic paralysis of both lower extremities, with a bilateral Babinski sign and ankle clonus, loss of abdominal reflexes and disturbance of sensation up to the seventh thoracic dermatome. Operation revealed a large extradural cyst, which was removed. Almost complete recovery of motor function and complete recovery of sensation followed in three months.

The following is presented as the characteristic syndrome of compression of the spinal cord by an extramedullary cyst: An adolescent boy or girl has a history and symptoms of a progressive spastic paraplegia. Pain is absent or inconspicuous. Sensory disturbances are slight and extend to the midthoracic region. Manometric tests show a subarachnoid block, with the spinal fluid changes characteristic of compression of the spinal cord. Roentgenograms show enlargement of the interpedicular spaces of three or more vertebrae, usually between the fourth and the tenth thoracic vertebra, with narrowing and atrophy of the pedicles of the affected vertebrae.

KUBITSCHEK, St. Louis.

CLINICAL DETERMINATION OF THE LIGHT THRESHOLD. EDMUND B. SPAETH, Arch. Ophth. **11**:462 (March) 1934.

In discussing the function of visual acuity one is inclined at times to speak too casually of perception of light, of color vision and of the perception and identification of form. One may fail, however, except when under the necessity of

considering details of retinal physiology, to differentiate retinal function into that which is purely ocular and that which is neurocentral, even of a subcortical nature. Thus, one may be vague and indecisive in separating retinal sensitivity and response into certain stages: (1) primitive perception; (2) that stage wherein there is an integration of recepts of a more highly discriminative pattern in which qualitative as well as quantitative details of the constituent sensations carry into consciousness factors such as attention and awareness, and (3) a "learning by experience" stage.

The first stage can be called a dyscritic stage; it is a purely primitive one wherein no discrimination or differentiation is present. The retinal recepts concerned give rise to changes in the stream of consciousness or, as the psychologist says, of psychoplasm, of such a kind that the cenesthesia (undifferentiated complex of organic sensations which make up that spoken of as vital sense) is raised in potential, giving rise to awareness. This phototropism is the response from that microscopic pigmented spot in certain minute unicellular forms of life, e. g., Euglena viridis (a flagellate), which enables them to advance or to recede from areas of greater or lesser illumination. With such an organism, perception of light is a trial and error effort in the search for food and comfort. This most simple of eyes is capable only of that function which is called perception of light. The verted eye of certain forms of life, such as the worm Stylaria lacustris, is another but more complex example. It is wholly separate and distinct from the second or epicritic stage. Parsons offers a definitive description of the latter form of perception: "The constellation of recepts [the stimulus and its ocular reactions] gives rise to a perceptual pattern in which cognitive elements are so differentiated that the diverse sensations are discriminated, awareness is focused upon those features of the pattern which are of significance and awareness becomes first attention and later experience." Thus, in terms of retinal sensation, is expressed the usual and highest form of usable visual effort and results.

Certain facts in the physiology of retinal function as they apply to the light sense are considered and discussed, and on them is based a plea that the study of the threshold of light should be considered of more importance from a clinical ophthalmologic standpoint. There are certain essentials, however, which must be completed before one can proceed with a satisfactory procedure. These essentials may be included in three general groups: The first group includes the size of the retinal image, its position, its chromatic stimulus, the intensity of light used, the area of the pupil and a necessary correction for differences in this. The second group should include the following: the necessity for preexposure or preliminary light adaptation and subsequent dark adaptation; dark adaptation at the fovea; the theoretical bases of, or opinions relative to dark adaptation; visual acuity during dark adaptation, and a standardization of adaptation. In the third group, logically, methods of testing would be discussed as to ease of operation, standardization of the results in an easily applied scale and the value of the test from a clinical standpoint. This group should include also standardization as to the length of time of exposure for the threshold illumination, and certain psychologic factors such as warnings, etc., which might be relevant should be controlled as well. Without their consideration, chaos will occur.

The apparatus which Spaeth has devised and has used for the past five years is by no means an accurate laboratory research machine—its limitations are definite —but it furnishes a constant means of conveniently obtaining valuable data. Purposely nothing has been said of the various other adaptometers, photometric systems, glasses, disks and lanterns which have appeared since the first published and valuable investigations of Arago in 1858. All have certain limitations, but at least one can obtain conveniently with the apparatus described something of inestimable value in diagnostic and prognostic procedures—something that has been neglected because of the inaccuracies, mechanical defects and difficulties connected with examination of the light minimum in the dark-adapted eye.

In a large number of pathologic conditions of the eyes examined for the light sense minimum, various findings remained constant for each type of case. Of these, the various types of glaucoma, atrophy of the optic nerve, papillitis, papil-

ledema, pigmentary disturbances of the retina and retinal and choroidal pathologic conditions all seem to have a relationship to the threshold of the light sense, which is more or less characteristic for each condition.

SPAETH, Philadelphia.

FATAL COMPLICATIONS OF OTITIS MEDIA: WITH PARTICULAR REFERENCE TO THE INTRACRANIAL LESIONS IN A SERIES OF TEN THOUSAND AUTOPSIES. CYRIL B. COURVILLE and J. M. NIELSEN, Arch. Otolaryng. **19**:451 (April) 1934.

Courville and Nielsen discuss autopsy observations in relation to the temporal bone with various subheadings such as infection of the meninges, abscess, thrombosis and encephalitis, and propose a plan for a postmortem study of cases under a number of headings. They have studied 10,000 autopsies at the Los Angeles General Hospital, which they have reported in a statistical study to be published in the *Acta oto-laryngologica*. The present article is concerned more particularly with the characteristics of the individual lesions, their interrelationship and their possible significance. The intermediate and transitional stages of intracranial lesions are frequently overlooked, especially those of mural thrombi. Occasionally the lesions are so varied that it is difficult to decide which is primary or what is their order of importance. A case is reported illustrating meningitis and otitis media associated with sinusitis, the sinusitis apparently being the actual source of the meningitis. Cases of this sort arising from ethmoid and sphenoid sinuses are discussed. Cases in which an abscess of the right parietal lobe was found, together with an infective thrombus of the right lateral sinus and a fistula from the middle ear, are discussed from the standpoint of the sequence of the lesions, and an effort is made to determine which lesion was primary. Otitis media is a frequent terminal lesion in infancy, either as a result of constitutional disease or associated with bronchial pneumonia, enteritis, acute exanthems, etc. Otitis media was found at 303 of 5,000 autopsies. The group is thoroughly analyzed from the standpoint of age and other lesions present and the complications found. The frequency of involvement of the petrous tip is, of course, carefully investigated, and three cases are reported illustrating petrositis and three illustrating thrombi or pus in the carotid artery. Intracranial complications of petrositis are discussed in detail. Extradural abscess usually indicates a fairly high degree of local resistance, which accounts for the fact that it is found so many times in operations with no other intracranial lesions. Statistics of frequency of extradural abscess arising at different parts of the temporal bone are given.

Subdural abscesses are classified on an etiologic basis in the following manner:

"A. Extension by direct continuity through the bone and dura: 1. Direct spread, with no local reaction from the point of penetration through the bone and dura, usually over the tegmen tympani (3 cases). 2. With active local reaction and walling off of a small subdural abscess, usually located between the posterior surface of the petrous bone and the anterior margin of the cerebellum (4 cases). 3. Secondary breaking down of adhesions about a dural fistula, leading to a superficial cortical ulceration (1 case) or to an abscess in the temporal lobe (1 case).

"B. By retrograde extension along venous channels: 1. Regional, about the inferior cerebral veins or (rarely) about the superior cerebellar veins, afferent channels of the lateral sinus which was thrombosed (3 cases). 2. Distant, consequent to extension to distant points of the thrombotic process originating in the lateral sinus; (*a*) extension to the cavernous sinus (1 case) or to the superior longitudinal sinus (1 case); (*b*) extension by way of the anastomotic venous system (1 case).

"C. Rupture of an abscess of the brain into the subdural space. 1. Spontaneous rupture (0 cases). 2. Postoperative rupture into the subdural space following attempts at drainage (1 case—posterior fossa)."

Subdural abscesses are often overlooked owing to the presence of other lesions. Seventeen cases are analyzed in relation to the lesion of the ear, and the association of sinusitis as a cause either in conjunction with otitis or as a separate entity is discussed. Charts and illustrations give classificaton of subdural abscesses and show

readily the various avenues of extension. Under "Thrombosis of the Intracranial Venous Channels," the various sites of the lesions are reported, with case histories illustrating intrasinus abscesses and illustrations showing various points in the body in which lesions might occur. A chart illustrating the various points in the brain, the site of complications of lateral sinus thrombosis, illustrates the text on this topic nicely. The pathologic lesions found in otitic leptomeningitis and otitic encephalitis, nonsuppurative encephalitis and abscess of the brain are discussed in relation to the type of lesion found and also the location. A protocol has been formulated for the study of postmortem material in cases with intracranial complications. Instructions are given for the exact procedure in examining the various parts. This thorough and interesting fifty page article cannot be adequately abstracted in a short space and should be read to be thoroughly appreciated.

HUNTER, Philadelphia.

SCHÜLLER-CHRISTIAN DISEASE (XANTHOMATOSIS). JOHN M. WHEELER, Arch. Ophth. **11**:214 (Jan.) 1934.

In 1930, Wheeler presented the syndrome of "exophthalmos associated with diabetes insipidus and with large defects in the bones of the skull" and described the case of a patient who was under his care at the time. He was able to establish definitely the cause of the exophthalmos by surgical exploration which disclosed xanthomatous nodules in the orbit. Previously, Schüller, Christian and others assumed that exophthalmos was caused by large defects in the roof of the orbits. In other words, they thought that the pathologic process had performed a decompression, with encroachment of the contents of the cranial cavity on the contents of the orbital cavity. In Wheeler's case, although the bony roof of the orbit was apparently absent, the periosteum was intact and in the proper place. The roof offered good resistance to pressure by the finger from within the orbit, and no pulsation was felt.

Since Wheeler's first report, he has operated on the same patient to remove a xanthomatous nodule from behind the right ear. He also found it necessary to explore the orbit again. Apparently, widespread fibrosis was in process, and the prognosis was grave.

A second patient under his observation died, and a pathologic study of the tissue was made. The microscopic changes are described in great detail. Some of the clinical findings are included here because of their interest:

The general appearance of the patient was that of an undersized, underdeveloped and emaciated white boy, aged 3 years, who was cachectic, apathetic and chronically ill. Marked exophthalmos and yellowish pallor were the most striking characteristics.

Dry scabs of infected eczematous lesions were present all over the scalp; impetigo was present over the back and on the left side of the thorax. The skin was pale, yellowish and dry; the mucous membranes were of a poor color.

There was marked exophthalmos, more in the right than in the left eye, with some swelling and ecchymotic discoloration of the orbital tissues on the right. Marked conjunctivitis and keratitis were present, with corneal opacity and purulent discharge from the right eye; the left conjunctiva, sclera and cornea were clear. The patient had no sight in the right eye but apparently had some perception of objects with the left. The movements of the eyes were not well performed, although there was no definite ocular palsy. The left pupil reacted to light.

All the teeth were missing except the upper incisors, which were loose, sordid and unhealthy. The gums were soft, irregular and retracted. There was no bleeding.

Roentgen examination of the entire skeleton, except the vertebral column, showed multiple sharply demarcated lesions of negative density throughout the bones of the cranium, both scapulae, the ribs, the pelvic bones, both femurs and the right humerus. Although these films were not taken for special detail of the mandible, definite similar defects were seen involving a large portion of the mandible. A single lesion was seen in the left fibula. The tibias did not show

definite changes. An anteroposterior view of the chest revealed an extensive patchy increase in density in both pulmonary fields, with apparent thickening of the pleura along the small interlobar fissure on the right.

Some of the outstanding microscopic observations at the time of the postmortem examination were: The same pathologic changes were seen in practically all tissue examined—the splenic pulp, the malpighian bodies, the liver cells, the thymus, the adipose tissues and striated muscle bundles, the pleura, various sections from the femur, the dura, the subepicardial fat, etc. In some of these the cells exhibited marked pleomorphism, and occasional mitotic figures were seen. Many cells were actively phagocytic. The cells were filled with small fat vacuoles; multinucleated giant cells were seen; deposits of cholesterol crystals were common, as was also the formation of new connective tissue. Active phagocytes were found, with erythrocytes, lymphocytes or hemosiderin in their cytoplasm. Small hemorrhages and areas of necrosis, and in the dura great numbers of large foam cells, were seen. An increase in collagenous connective tissue was general. Lymphoid follicles were absent; in all tissues the droplets seen stained with scarlet red.

SPAETH, Philadelphia.

VESTIBULAR FUNCTIONS OF THE FRONTAL LOBE WITH THE STRIATE BODY: CEREBRAL AND SUPRATENTORIAL ATAXIA. L. J. J. MUSKENS, Rev. d'oto-neuro-opht. **12**:161 (March) 1934.

In this article Muskens analyzes the reports in the literature of frontal ataxia with forced movements and attitudes (oculogyric crises and analogous phenomena so far as they are in relation with frontal ataxia) occuring in the frontal and horizontal planes in man. The notion that forced movements are caused by cerebellar disturbances (Luciani) was questioned by later writers, and new studies of forced movements were undertaken. These studies brought out the important rôle played by the posterior longitudinal bundle and the commissural nuclei and their relations with the pallidum. Following the appearance of postencephalitic parkinsonism, neurologists were forced to a more thorough study of forced movements of supravestibular origin, and a renewed investigation of the anatomy and physiology of the cerebral trunk was made. The nomenclature of the direction of the movements of rotation has led to confusion because it is different for the same movements, depending on whether the observed animal is viewed from in front or behind. In certain cases of disease of the vestibular system in man, complete rotation with deviation of the eyes has been observed. In cases of a focus in the thalamus or striate body, rotation is probably never observed; only falling to the opposite side is seen. In five of Gerstmann's cases of unilateral gunshot wound of the frontal lobe there was falling to the sound side; undoubtedly there was softening of the anterior portion of the globus pallidus. In 1914, Muskens showed that after a lesion of the striate body in quadrupeds there was a marked tendency toward falling to the sound side; other experiments had shown that hemisection of the cerebral trunk behind the posterior commissure caused falling or rotation to the injured side. In 1918 the following clinical rule was enunciated: "In the case in which this symptom (i. e., falling to the right) exists as a consequence of a lesion situated orally from the posterior commissure, this lesion, according to our experimental findings, must be localized in the optic thalamus or the striate body on the left side. . . . Falling to the sound side is an important manifestation of lesion of the anterior part of striate body."

Mouvements de manège are not noted in man as easily as the tendency to rotation or falling. Roussy called attention to *mouvements de manège* after a thalamic lesion, but anatomicophysiologic and clinical analyses do not make clear the anatomicophysiologic relations of locomotion and their dependence on the posterior longitudinal bundle, the commissural nuclei and the globus pallidus. According to C. and O. Vogt, the pallidomesencephalic pathways are the final common path for both thalamopallidal and thalamostriopallidal reflexes. The importance of these pathways for ocular movements, as well as for locomotion, is recognized. The conclusion of the Vogts that athetosis, choreic movements, forced

laughter and spasms of twisting and trembling are hypothalamic hyperkineses is accepted. Recently neurologists have tended to attribute symptoms related to supravestibular signs to a hyperexcitability or hypo-excitability of the vestibule, leaving out of consideration the fact that hyperexcitabilty of the supravestibular pathways and nuclei may be simulated by unilateral interruption of a bilateral pathway. In such cases labyrinthine examination may lead to false deductions.

Conjugate deviation of the head and eyes in man may be considered to be identical with *mouvements de manège*. As previously demonstrated, in a unilateral lesion of the cerebral trunk up to the level of the anterior quadrigeminal bodies, *mouvements de manège* occur from the diseased to the sound side; if the lesion involves the thalamus, external lamina of the thalamus or striate body, globus pallidus or putamen, these movements are always toward the diseased side; when the lesion involves the posterior longitudinal bundle, the movements to the sound side are more violent and long lasting. DENNIS, San Diego, Calif.

FOVEAL PROJECTION DURING DUCTIONS. ROBERT H. PECKHAM, Arch. Ophth. **12**: 562 (Oct.) 1934.

Because of the difference in the language or the terminology used by psychologists from that used by ophthalmologists, it is somewhat difficult to express ideas which have the same ultimate meaning to both groups. This difference is primarily due to the diverging purposes of the two branches of science. Consequently, when data have been found which are not consistent with past theory and are eventually challenging to methods of practice, it is with considerable reluctance that these findings are circulated in psychologic terms before some additional or replacing elements have been found to supplant any changes indicated as necessary. And yet there are certain aspects to the present accumulation of data that make it necessary to publish them. It is more in the nature of a questioning or warning than in the nature of criticism that this paper was prepared.

A comparison has been drawn, from the knowledge of optics, between the eye and the camera, and the retinal image has been considered as similar to the camera image and the retina as similar to a photographic plate. How dangerous the comparison can be, if it is carried too far, is understood by all, although it is most useful in introducing the study of physiologic optics to younger students.

From this crude analogy, from other unverified observations, from spasmodic knowledge of tumor localization and from the histologic study of dead and artefact retinal tissue and the tract of the second nerve, Peckham believes that gross liberty has been taken in developing a theory of binocular fusion and ocular movement.

It was the author's desire to begin a series of investigations which would determine the movement of the eyes during binocular vision, so planned that even though one is unable to dissect out the fovea in a living human specimen one can at least conjecture the accuracy of its position from the behavior of the eye and its perceptual responses.

Convergence and ocular movements have been measured in a manner which, while hardly more accurate than the methods of the past, is at least adequate to show up certain deficiencies in the theory. These observations have definitely indicated that both foveae are not always under the images of the objects of regard, when this object is fixed with both eyes. Under the various conditions of the author's investigations, the subjects studied reported binocular vision as present in conditions when the images were on the opposite sides of the two foveae. Further, under the conditions of the author's experiments, there was in many cases a difference of as much as 4 or 5 degrees between the two fixations, and yet these fixations should have been identical. The subject here also reported single binocular vision.

In attempting to explain this disparity of foveal fixation in its relationship to binocular vision, the author states: "When the ductions of the patient are measured, it has been claimed that one is measuring the amount of independent movement of which the eyes are capable. But this has not been done; a measurement of the

movement has been obtained, but it is subject to the amount of disparity or retinal difference which the patient will tolerate. When what has been called relative convergence and also what has been called accommodative convergence are measured, the amount of movement which has occurred in fact has not been measured accurately."

Peckham closes with a moral to the effect that while duction tests are not useless their results should be regarded with question as indicative of what has happened during the test but not as a measure of the fact. Since he offers no substitutes, his closing sentence is especially valuable. One can at least regard the findings of the phoria tests and the duction tests with considerable care, understanding that their value lies not in their accuracy but in their interpretation.

SPAETH, Philadelphia.

THE CHOLESTEROL CONTENT OF THE CEREBROSPINAL FLUID. B. HOLTHAUS and B. WICHMANN, Arch. f. Psychiat. **102**:147 (June) 1934.

The method employed by Holthaus and Wichmann for the study of the cholesterol content of the cerebrospinal fluid is based on the one used by Bloor, Allen and Pelkan. For the final determination and computation, however, a modification is suggested in which use is made of the Pulfrich graduated photometer. The authors are of the opinion that the usual colorimetric determinations are not reliable enough, especially when small quantities of cholesterol are involved. They have determined the cholesterol content in a large number of normal persons and of persons suffering from various nervous and mental diseases.

In normal persons, in those with psychopathic personalities and in neurasthenic and hysterical patients the content varied between 0.3 and 0.6 mg. per hundred cubic centimeters. The authors consider these limits as normal variations. The large majority of patients with dementia paralytica, both treated and untreated, showed an increase in the cholesterol content to more than 0.6 mg. and in some it reached as high as 1.03 mg. This increase did not seem to be related to the other findings in the spinal fluid, as in some cases in which other tests showed disturbances of the fluid the cholesterol content was within normal limits. In cases of tabes no deviations from the normal were found. In cases of other syphilitic diseases of the central nervous system there was a slight rise in the amount of cholesterol. In cases of meningitis there was a pronounced rise, the content in one case reaching as high as 8.84 mg. Here there seems to be a certain relationship between the high cell count and protein content and the cholesterol content. In cases of epilepsy the variations were from 0.3 to 1.27 mg. Increased cholesterol content may be found in cases of idiopathic as well as of organically conditioned epilepsy. There was no relationship between the findings in other tests of the cerebrospinal fluid and the amount of cholesterol, and the absence or the presence of positive encephalographic findings showed a similar absence of relationship. In the cases of pyknolepsy there was some rise in the cholesterol content. In cases of hydrocephalus there was a tendency toward a rise, although in one case in which there was a marked hypersecretion of the spinal fluid there was a fall of 0.21 mg., this being the only case in which the cholesterol content was lower than normal.

The most marked changes in the cholesterol content were found in cases of tumor of the brain, the quantity in one case reaching as high as 47.8 mg. Here, too, there did not seem to be any very definite relationship between other spinal fluid findings and the cholesterol content, although a very high cholesterol content was found in cases in which there was also a very high increase of the total protein content. Some increase in the cholesterol content was also found in cases of cerebral arteriosclerosis, of postencephalitic disturbances and of other organic lesions of the brain. There was an increased cholesterol content in ten of twenty-five cases of schizophrenia, the highest quantity being 0.96 mg. The high cholesterol content was found in cases in which there had been previous disturbances or in which the disease was of long standing. In cases of diseases of the spinal cord, especially those associated with marked disintegration of tissues, there was also an

increase in the cholesterol content. In cases of diseases of the peripheral nerves there was no deviation from the normal.

The conclusions are that an increase of the cholesterol content of the spinal fluid is frequently to be found in cases in which diseases of the organic brain are present, although no relationship can be found between such increase and disturbances in the spinal fluid as shown by other tests. MALAMUD, Iowa City.

NERVOUS FITS OF ADOLESCENTS—CLINICAL DIFFERENTIATION AND PHYSIOLOGIC RELATIONSHIP BETWEEN EPILEPTIC FITS AND PSYCHONEUROTIC FITS. H. BARUK, J. belge de neurol. et de psychiat. **33**:139 (Feb.) 1933.

Baruk considers that convulsive attacks occurring in adolescent boys and girls comprise a distinct group; he divides them into two subgroups, the epileptic and the nonepileptic fits. In the group of epileptic fits he makes a further subdivision into the convulsive and the syncopal fits, which, with or without aura, are associated with loss of consciousness, cyanosis and vasomotor manifestations. In addition, there may be convulsive movements of clonic and tonic types. He concludes that the characteristics of a convulsive fit are important but not absolute and may be partially or almost totally lacking. He described the syncopal forms as those associated with loss of cognitive function and not associated with convulsive movements; they may occasionally be confused with cardiac attacks. He describes further the epileptic psychic equivalents, which consist only of an aura. He thinks that this type of disturbance is more common in young persons and adults than in children. He describes a condition which he calls the "absence," which is, apparently a type of petit mal attack; it is associated with only a momentary loss of cognitive function and may occur many times during the day. He states that this type of seizure may be associated with various muscular disorders, such as loss of ability to stand, and a type of attack that is described as cataplexy. This may also be associated with complex acts. Further subdivisions of epileptic seizures are the attacks of dreams, in which there is a psychic automatism, a pseudo-emotive attack in which the patient carries out some purposeful act, though without having any purpose, and the vegetative or visceral attacks associated with nausea, vomiting or excessive salivation. He believes that there is a striking parallelism between acrocyanosis and epileptic attacks, considering acrocyanosis to be a sort of autonomic epileptic equivalent.

In the nonepileptic group are placed cases of cataplexy, in which the attacks may be brief or prolonged, even as long as a day or more; lipothymic or syncopal seizures, in which a mild seizure may be brought on by slight shocks, and attacks of automatism, which are differentiated from those of the epileptic variety because they disappear after the patient is reprimanded. Dream states may also occur as a nonepileptic attack in children of "nervous temperament"; these occur usually when the child is alone and may seem to be hallucinatory. Attacks may ensue on emotional stimuli. Baruk describes an attack of a hysterical nature, which he says is relatively infrequent and is not of serious import. In this same group he describes nonepileptic vegetative and visceral attacks associated with headaches, nausea, vomiting and occasionally diarrhea.

In brief, he differentiates the epileptic attacks from the nonepileptic by the suddenness of the seizure and the violent disturbance of organic and vascular function, while the nonepileptic are characterized by a less abrupt beginning and a premonition of an oncoming attack; they are essentially dependent on such factors as emotional disturbance, fatigue, overwork, etc. In this class also there is no real disappearance of the cognitive function. Baruk concludes that from the pathogenic and the physiologic standpoint these aberrations are merely different manifestations of the same disorder and are evidences of the same type of pathologic change in the nervous system. He calls attention to the fact that similar mechanisms can be produced in experimental animals by the administration of certain toxic substances. WAGGONER, Ann Arbor, Mich.

THE COMPONENTS OF THE RETINAL ACTION POTENTIAL IN MAMMALS AND THEIR RELATION TO THE DISCHARGE IN THE OPTIC NERVE. RAGNAR GRANIT, J. Physiol. **77**:207 (Feb. 8) 1933.

Leads from the cornea and a decerebration wound were taken to the input of a directly coupled amplifier with a string galvanometer in the output. The aim of the work was to try to establish a biologic analysis of the complex action potential of the retina. This was done in two ways: by giving the animal ether and by interfering with the blood supply of the retina. Both agents were found to affect certain components selectively and in a reversible manner.

The complex retinal potential arising in the retina on stimulation with white light was found to develop in that part of the sense organ which histologically is a "true nervous center" (Cajal). It appears after a latent period involving synaptic interaction and hence cannot have arisen distal to the locus where the first synapses occur. The complex effect is an algebraic sum of three components, the properties of which may be summarized as follows: The first process, P I, rises slowly after a long period of latency and falls in a similar manner. It is positive in the usual representation of the retinal action potential. P I is easily removed by the administration of ether. Before the process begins to diminish it may, however, pass through a temporary stage of enhancement. Likewise, after withdrawal of the narcotic it is often temporarily enhanced in good preparations. Slight asphyxia often favors P I. In the dark-adapted cat the first process is present only with large areas and high intensities of stimulation. The second process, P II, rises rapidly as the positive *b*-wave of this complex response; it falls rapidly at high intensities and less rapidly at low intensities and continues hidden by the first process under the *c*-wave of the complex action potential. It is the only process that can be detected at all intensities capable of giving a detectable response and is of the same sign as the potentials recorded from the eyes of nonvertebrate animals. This component is associated with the production of impulses. P II is selectively affected by asphyxia and can also be removed during prolonged narcotization with ether. The fall in the *b*-wave probably represents, partly at least, a process of adaptation, but it is also dependent on the third process, P III. This process is of negative sign and therefore by algebraic summation influences the amount of potential in the complex response. P III first appears as the *a*-wave of the composite potential; its further course is hidden, but by its return to zero on cessation of the stimulation the positive off-effect is elicited as a release phenomenon. The off-effect has its counterpart in a renewed discharge through the optic nerve. This is held to imply that when P II is released from the negative P III, it is being released from a process in some way concerned with the inhibition of impulses. By definition the off-effect is then a "post-inhibitory rebound." P III is the most persistent of the components of the retinal action potential.

The author makes one generalization, i. e., the necessity of realizing that the retina as a sense organ cannot be identified with the rod-cone reception system. The synaptic apparatus continuously modifies the primary response determined by the properties of the receptors. Considering the complications present already at the "subsensational stage," more work with the retina rather than with sensations appears to be necessary for the establishment of retinal physiology on a sufficiently broad and unprejudiced basis.

ALPERS, Philadelphia.

CLINICAL MANIFESTATIONS OF INTRACRANIAL ANEURYSMS. F. J. NATTRASS, Lancet **2**:915 (Oct. 21) 1933.

In the largest group of cases intracranial aneurysm gives no indication of its presence until it leaks or ruptures. It is one of the commonest causes of extracerebral or subarachnoid hemorrhage. Such an accident may occur at any age, and while rupture is apparently rare in childhood many of the patients are in adolescence. The clinical picture is produced by the sudden effusion of blood into the subarachnoid space, primarily and predominantly at the base of the brain, and

the severity and duration of the symptoms depend on its arrest or continuance. Typically, the patient is seized with a violent pain in the head, and temporary unconsciousness may ensue. A history of some physical effort, as during straining at stool, is present in some cases. There usually is considerable mental confusion and excruciating headache; vomiting is persistent. A few hours later the patient shows signs of meningeal irritation. The pain locates itself in the occipital region and down the spine. The patient tends to lie curled up and is resentful of interference and of light. A definite degree of rigidity of the neck develops, and Kernig's sign is elicited; frequently the deep reflexes are lost, and the plantar responses are of the extensor type. Some elevation of temperature commonly occurs. A diagnosis, however, cannot be other than tentative until lumbar puncture has been done and blood is found in the cerebrospinal fluid.

The subsequent course in these cases is extremely variable, but generally complete recovery requires several weeks; there is always the danger of recurrence of hemorrhage with the reappearance of symptoms of compression.

Certain additional clinical features are of much interest and of diagnostic importance. A large amount of albumin is occasionally present in the urine immediately after the hemorrhage; the explanation is uncertain, but Symonds accepts as probable the disturbance of nerve centers concerned with renal secretion. Much commoner, however, and of great diagnostic value is the appearance, in association with subarachnoid hemorrhage, of large preretinal or subhyaloid hemorrhages. These are undoubtedly due to the extension of blood along the arachnoid sheaths of the optic nerves and the leaking of blood under pressure through the lamina cribrosa. Papilledema and retinal hemorrhages may also occur if the increased intracranial pressure is prolonged sufficiently. Last, the mental symptoms which frequently accompany the prolonged convalescence in many cases are rather characteristic. A general failure of attention and memory is common, but the most remarkable mental picture is the Korsakoff-like syndrome. This is identical with that seen in some cases of polyneuritis, especially alcoholic, and is characterized by disorientation for time and place, and by organized delusions or false reminiscences on which the patient enlarges freely.

There is a small but confusing group of cases in which an aneurysm may cause frequent small hemorrhages. This gives rise to mild signs of meningeal irritation which are misinterpreted easily as rheumatic stiff neck or lumbago. Diagnosis of unruptured intracranial aneurysm is possible, and indeed not difficult, in some instances in which the aneurysm arises from the internal carotid artery where it joins the circle of Willis.

BECK, Buffalo.

CULTURE AND MENTAL DISORDER. A. IRVING HALLOWELL, J. Abnorm. & Social Psychol. **29**:1 (April-June) 1934.

If mental disorders in different cultures are to be thoroughly understood, the feelings, thoughts and behavior of persons in a specific community must be analyzed and evaluated. Hallowell considers some material which came to his attention while doing field work among the Berens River Saulteaux of Manitoba and Ontario. He here had an opportunity to consider the normal in this particular culture, and he found that the character and incidence of at least certain classes of mental derangement bore some relation to the culture or pattern. Cooper is quoted as suggesting that the "wihtigo psychosis" of the Cree and "running amok" among the Malays are somehow intrinsically related to the respective cultures of these people. Perhaps the same mental disorder may occur in different cultures, but the particular form which its symptoms take may be a reflection of these cultural differences. In order to illustrate some of the problems involved in the diagnosis and etiology of mental disease of individual persons, a case from the author's own series is quoted, a case of mild zoophobia. W. B., an Indian, who was an excellent hunter and accustomed to handling all sorts of animals, was subject to the fear of toads. The thought or sight of these animals threw him into a panic and rendered him sleepless. Since other Indians deliberately teased him by placing toads near him

it seemed apparent that his individual fear of them was exaggerated, though there was a generalized belief among the entire native population of the malevolent attributes of toads, and the presence of toads indicated to them that a tabu had been broken. As this particular Indian had been converted to Christianity, he was perhaps suffering from a religious conflict. The general question, then, is brought up as to the possibility of higher incidence of mental disorders in cultures which are not at equilibrium, e. g., those going through the process of religious transformation through missionary efforts. C. G. Seligman observed no true cases of mental disorders in the villages of Papua, where the natives were living their own undisturbed life, but he does record psychoses occurring "as the result of stresses set up by white influence" as the consequences of race and religious conflicts.

Discussing the "wihtigo psychosis" (a cannibalistic obsession) described by Cooper as associated with the Cree Indians, Hallowell thinks that if the cases had been well investigated the wihtigo psychosis might have been relegated to a variety of generic types of mental disease comparable with those of other cultures, while others might prove to be only mildly abnormal. The wihtigo psychosis appears to be a morbid state of anxiety on the part of a subject directly traceable to the native interpretation of certain physical symptoms, such as distaste for ordinary food, nausea and vomiting, and a state of anxiety that develops when these symptoms appear. The reaction of the community to the symptoms because of the community's own projected fears and the vicious circle that is hence set up isolating and setting apart this unfortunate person actually cause a mental aberration. The author observed a case in which preliminary symptoms were treated rationally by an intelligent white observer and recovery was rapid.

WISE, Howard, R. I.

INTERMITTENT OBSTRUCTION OF THE FORAMEN OF MONRO BY NEUROEPITHELIAL CYSTS OF THE THIRD VENTRICLE: SYMPTOMS, DIAGNOSIS AND TREATMENT. BYRON STOOKEY, Bull. Neurol. Inst. New York **3**:446 (March) 1934.

Stookey protests against the general tendency of indiscriminately including diverse types of neoplasms with true intraventricular tumors in studies of tumors of the third ventricle. In an effort to determine a more definite symptomatology for primary tumor of the third ventricle, the study is based on a group of tumors arising within the third ventricle and having a fairly uniform point of origin and and common biologic characteristics, the so-called colloidal cysts of the third ventricle. The report is based on a study of thirty-four cases previously reported and three cases from the Neurological Institute. Attention is called to the dominance of the diencephalon over visceral functions through its connections with the sympathetic nervous system, and the relationship between pathologic changes in this region and disturbance of sleep, temperature, carbohydrate, water and salt metabolism and cardiovascular, pilomotor and ocular symptoms.

The probable point of origin of these tumors is discussed. The age incidence is largely between 20 and 50 years (88 per cent). Paroxysmal attacks of violent frontal headache and papilledema may be the only clinical signs of the condition. The headache differs from that common in other intracranial tumors in that it is more intense, and between attacks the patient is apparently entirely free from symptoms. This is due to the intermittent acute obstruction of the foramen of Monro or of the opening into the aqueduct of Sylvius, causing acute ventricular hydrocephalus. In 39 per cent of the cases striking relief was obtained by a change of position of the head. In 90 per cent of the cases symptoms of increased intracranial pressure (headache, vomiting and papilledema) were present. Of twenty-three cases with most complete records, localizing signs referable to the diencephalon were noted. The developmental sequence of symptoms is considered of greatest importance in differentiating primary tumors of the third ventricle from tumors of adjacent regions. Ventriculography and encephalography are considered of greatest value in establishing or confirming the diagnosis. Symmetrical, dilated lateral ventricles, with no air in the third ventricle, are usually found when

the foramen of Monro is obstructed. Personal experience in the use of these diagnostic tests is related in detail, with illustrative plates. Case records of the three cases from the Neurological Institute are given.

In discussing operative procedures, preference is given to an approach through the lateral ventricle over that through the corpus callosum; to evacuation of the cyst by suction before removal, and to a one-stage rather than a two-stage operation. In this series eight operations were performed. In one case a suboccipital craniotomy was done in a search for a cerebellar tumor; in another a subtemporal decompression was done as a palliative measure. Six exposures of the third ventricle were made with successful removal of the tumor. The operative mortality was 33.3 per cent, a rate which the author believes will be reduced in the future.

KUBITSCHEK, St. Louis.

GENICULATE GANGLIONITIS (HUNT'S SYNDROME): CLINICAL FEATURES AND HISTOPATHOLOGY. J. L. MAYBAUM and J. G. DRUSS, Arch. Otolaryng. **19**: 574 (May) 1934.

A case of inflammation of the geniculate ganglion is reported and discussed which illustrates the symptomatology of this disease with deep-seated pain in the ear associated with infranuclear facial palsy and herpes of the external canal. This report of the case is important in that it includes a histopathologic description of the seventh, eighth and fifth nerves, including the geniculate ganglion. The patient had some disturbance of the sense of smell, pain and swelling of the tissues around the right eye, partial paralysis of the right side of the face and total deafness in the right ear, pain in the throat and difficulty in swallowing and pain in the sacral region and the right leg. These acute symptoms had been observed for six weeks, but the hearing had been diminishing for a year and a half; the temperature was 101 F. On examination, the entire right side of the head was swollen, but both middle ears were normal on inspection. There was total loss of hearing in the right ear, and slight impairment was present in the left. For six weeks after admission, the patient was treated for marked maxillary sinusitis; at the end of this time pain suddenly developed in the left ear, with a bleb on the tympanic membrane and one on the auricle and pinna and a thin purulent discharge from the left middle ear. Epididymitis developed on the right side, and the infection gradually progressed until death occurred three months after admission. The cells of the left geniculate ganglion showed marked disintegration and change of the internal structure. The seventh nerve showed similar changes, with numerous gitter cells arranged in parallel lines or forming solid groups, often whorls. The left eighth nerve showed moderate degeneration, with occasional gitter cells. No marked changes were seen in the meningeal covering of the nerve. Scarpa's ganglion was degenerated. The left gasserian ganglion showed no obvious alterations in the ganglion cells, and no accompanying fibers were noted. The geniculate ganglion, the seventh and eighth nerves and the gasserian ganglion on the right side were normal. This is an important finding; it is not discussed at length by the authors but is of great interest to those who have followed the discussion of Hunt's syndrome, especially with relation to the source of pain in such cases. The authors could well have pointed out that the opinion held by Mills and others at the time that J. Ramsay Hunt published his paper, "The Symptom-Complex of the Acute Posterior Poliomyelitis of the Geniculate, Auditory, Glossopharyngeal and Pneumogastric Ganglia" (*Arch. Int. Med.* **5**:631 [June 15] 1910), namely, that the pain was due to involvement of the third nerve, was not borne out in this case. The left ear presented a labyrinthitis which may have been due to periarteritis nodosa from which the patient had been suffering and also a patch of otosclerosis in the region of the oval window but no fixation of the stapes. A discussion of the various points in Ramsay Hunt's paper follows. This is an interesting and instructive case report which should be saved for reference by those interested in Hunt's syndrome.

HUNTER, Philadelphia.

THE LOCALIZATION OF THE GUSTATORY CENTER. HENRY MARCUS, Acta psychiat. et neurol. **9**:85, 1934.

The cortical localization of the gustatory center has not yet been established. Gustatory cortical representation being bilateral, a complete deficit of this function can be expected only when the gustatory sphere is destroyed bilaterally. Such symmetrical lesions are extremely rare. On the other hand, irritative phenomena such as gustatory hallucinations and auras may be produced by a unilateral lesion in the vicinity of the gustatory center of one hemisphere. Such cases are not infrequent and offer better material for anatomicoclinical correlative study. Marcus reports such a case, in a man aged 40, who at 15 years of age had been accidentally shot in the head, a small lead shot becoming lodged in the dura on the right side of the sella turcica, where it was disclosed by roentgen examination. At the age of 20, he began to have epileptic absences, and eventually he had complete epileptic seizures. These always set in with gustatory hallucinations (as a curiosity, a taste of lead), occasionally associated with olfactory hallucinations. The seizures increased in frequency. The patient was operated on and died following a hemorrhage from the cavernous sinus. Autopsy disclosed a lead shot lying in the dura at the level of the floor of the sella turcica; the right uncus was flattened, and its anterior tip was depressed to the midline. The groove between the uncus and the fusiform gyrus was deepened, forming a pocket. On the mesial surface of the uncus, at the point of its transition into the gyrus hippocampi, the pia was thickened, the blood vessels were increased, and the root of the right third nerve was destroyed. Otherwise the brain and the brain stem were normal. The right temporal lobe, with the hippocampus and the cornu Ammonis, was studied histologically in serial sections. The lesion, which consisted of a glial scar, did not exceed 1 cm. in diameter and was confined to the cortex of the gyrus hippocampi. The cortex of the middle ventral portion of the gyrus hippocampi was destroyed, whereas the dorsomesial portion of the gyrus (subicular and presubicular areas) was entirely free from changes. Referring to the views of von Economo, who regarded the granular allocortex of the dorsomesial wall of the gyrus hippocampi as belonging to the gustatory sphere, Marcus expresses the belief that his case strongly supports this localization. The glial scar destroying the ventral portion of the gyrus acted as an irritative lesion on the neighboring dorsomesial area of the gyrus and discharged the gustatory aura. The discharge occasionally spread orally and, involving the uncus, gave rise to olfactory hallucinations.

YAKOVLEV, Palmer, Mass.

VERIFIED BRAIN TUMORS: END-RESULTS OF ONE HUNDRED AND FORTY-NINE CASES EIGHT YEARS AFTER OPERATION. W. P. VAN WAGENEN, J. A. M. A. **102**:1454 (May 5) 1934.

In Van Wagenen's follow-up series of 149 cases of verified tumors of the brain there were 80 cases of glioma. The patients lived an average of 38.8 months following operation. The period of useful activity of the group is estimated to be 24.4 months. There were 59 examples of encapsulated tumor of the brain and 4 instances of tumor of the blood vessel. This group of 63 patients had a survival period of 76.4 months and a period of useful activity of 59.3 months. Four patients with a metastatic tumor of the brain lived an average of thirteen months, with a useful period average of three months. One patient with a congenital heterotopia of the cerebellum has lived eight years, with a useful period estimated as nil. One patient with a pinealoma died following an operation directed toward its removal. The author believes that a new form of treatment for the rapidly growing primitive cell type of glioma typified by the glioblastomas and medulloblastomas must be sought for and found if the period of "useful activity" is to be of a reasonable duration. The end-result of the treatment of the encapsulated tumors—the congenital cysts, the meningiomas and the acoustic neurinomas—is almost in direct proportion to the promptness in diagnosis and treatment after the first symptoms. With competent surgical measures, a considerable period of "useful activity" is

assured and undoubtedly will be increased as years go by. The cerebellar gliomas, the astrocytomas, are favorable to operation. While there will always be a certain group of cerebral gliomas which, by right of their location or inaccessibility or growth potentialities, will carry with them a short period of "useful activity," their number should be a constantly diminishing one. If one is inclined to comparisons, it may be said that surgical treatment for tumors of the brain suffers not at all, and in fact stands out, as compared to that for tumors of the long bones, breast, stomach, esophagus and rectum. In view of the fact that twenty-five years ago tumors of the brain were almost invariably universally considered hopeless, the foregoing periods of "useful activity" lend a great deal of encouragement and hope for what may be accomplished during the next twenty-five years.

[J. A. M. A.]

SOME OBSERVATIONS ON THE INCIDENCE OF SCHIZOPHRENIA IN PRIMITIVE SOCIETIES. ROBERT E. L. FARIS, J. Abnorm. & Social Psychol. **29**:30 (April-June) 1934.

Statistics show that schizophrenia and other mental diseases based on a "shut-in" type of personality are found to be sharply concentrated in those sections of Chicago characterized by high mobility and social disorganization. Many different racial and national groups flow through this area, and yet the high rate of incidence of schizophrenia remains. Hence it appears that the explanation is to be found in the social situation prevalent in that area rather than in the racial traits of those inhabiting that particular section. Negroes who are living there show a greater incidence of schizophrenia than those who settle in better organized sections of Chicago.

An examination was then undertaken to attempt to find how the same race in the original primitive African culture would show a low incidence of the mental disease. Ellsworth Faris, during his expedition to the Belgian Congo in 1932-1933, failed to find any trace of a mental disease based on a "shut-in" type of personality. A few references made it possible further to check this finding. C. C. Seligman in his "Temperament, Conflict and Psychosis in a Stone-Age Population" mentioned no evidence of schizophrenia, and C. Lopes in his study of the natives of Brazil found that the wild peoples of the Brazilian interior include few psychotic persons in their number and that those present were more likely to be of the cyclothymic type. J. E. Dhunjibhoy found schizophrenia to be known in India but to be more common among the communities highly advanced in Western civilization, and F. H. G. Van Loon in his study of Malay life made no mention of schizophrenia. He spoke only of that type of mental aberration known as "running amok."

It seems to be established, therefore, that schizophrenia may result in primitive people, but the persons affected are usually found in the urban centers, whereas truly primitive people are practically free from the disorder. There seems, then, to be a relationship between schizophrenia and the lack of opportunity for sufficient intimate, sympathetic and personal social contacts. WISE, Howard, R. I.

THE POSSIBILITIES OF REGENERATION IN EXPERIMENTAL NEURITIS PRODUCED BY LEAD INTOXICATION. J. M. DE VILLAVERDE, Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:317 (June) 1933.

Unlike most toxins, lead intoxication is followed by little evidence of regeneration. Villaverde attempted to determine what doses of lead were necessary to produce neuritis, and whether there was regeneration of fibers after it, or whether no regeneration followed the intoxication. Two rabbits were given subcutaneous injections of lead acetate (1:1,000). After a time evidence of nervous disturbances developed, and the injections were continued for a long time.

There were no changes in many nerve fibers. Others showed definite lesions without any evidence of regeneration. All parts of the nerve fiber were affected—Schwann cells, neurofibrils, etc. The latter showed loss of individuality. Doinikow believes that the Schwann cells are the first to be affected by the toxin, but Cajal

and others have shown that the vacuolation of these cells is often normal. Villaverde found all parts of the nerve affected, often to a high degree. The Schwann cells particularly are affected, their nuclei becoming atrophic and their protoplasmic prolongations being shrunken. These changes, to a lesser degree, are seen in cases of early intoxication from lead. The effect on the Schwann cells is not always the same, though they are always affected by the lead. The myelin structure is likewise affected. The trabeculae which are visible within the myelin sheath appear torn and take the silver stain irregularly. Elsewhere they appear shrunken. Not only the middle layer but also the outer and inner layers of the myelin sheath are affected in this way. The incisures of Lantermann are changed. The Golgi apparatus is markedly changed and in some instances is no longer recognizable. The axons are markedly changed. After a relatively long period there are attempts at regeneration of the axis-cylinder, with the formation of new side processes.

ALPERS, Philadelphia.

VITAL NEED OF THE BODY FOR CERTAIN UNSATURATED FATTY ACIDS: IV, V AND VI. H. M. EVANS, S. LEPKOVSKY and E. A. MURPHY, J. Biol. Chem. **106**:431, 441 and 445 (Sept.) 1934.

The authors present papers IV, V and VI of the series on the "Vital Need of the Body for Certain Unsaturated Fatty Acids." The reproduction and lactation of rats on fat-free diets have been investigated with a large number of rats. The conclusions are as follows: 1. There occurred a characteristic prolongation of gestation time of from one to three days, together with impairment of the birth mechanism. Small litters of undersized young were born dead or so weak that they died soon after birth. In a fifth of the cases there was failure to litter after a positive placental sign (resorption). Some maternal mortality was encountered. The addition of the essential unsaturated fatty acids resulted in marked improvement in all the abnormalities indicated. When all the known vitamins were added in increased amounts, lactation on the fat-free diet plus the essential unsaturated fatty acids was possible, but not highly successful, the weights of the young at weaning being still subnormal. Inclusion of 25 per cent lard or butter fat, however, gave weights at weaning approaching normal, and diets of neutral foodstuff could not confer greater improvement.

2. Gestation is unsuccessful on diets with saturated fatty acids (hydrogenated coconut oil) as the source of energy, when vitamin F (the essential unsaturated fatty acids) is absent. The addition of vitamin F enables successful gestation to occur. Lactation is not normal even when all the known supplements are increased.

3. Males on fat-free diets invariably become sterile. The addition of small amounts of essential unsaturated fatty acids can cure as well as prevent this sterility.

MARY DAILEY IRVINE, Boston.

METASTATIC SPINAL EPIDURAL ABSCESS: REPORT OF CASE WITH RECOVERY FOLLOWING OPERATION. R. F. SLAUGHTER, F. FREMONT-SMITH and D. MUNRO, J. A. M. A. **102**:1468 (May 5) 1934.

The authors present a case of spinal epidural abscess in which complete recovery followed early and adequate drainage of the spinal epidural space, which illustrates the following point: Acute spinal epidural abscess is a definite clinical entity that can be recognized before the onset of compression of the spinal cord. The diagnosis must be confirmed by the demonstration of a subarachnoid block by means of a lumbar puncture. The mortality from meningitis brought on by this procedure is certainly no greater and may well be less than the inherent mortality of the disease plus the mortality that results from delayed treatment. The onset of the disease is characterized by the occurrence of a sudden severe pain in the back, which tends to radiate into nerve root fields. There is a varying degree of systemic toxemia such as accompanies any major infection of soft tissues in which drainage is not employed. A history of either a recent healed or an active unhealed staphylococcic infection is confirmatory evidence. The diagnosis is established and

treatment indicated following the demonstration of pus in the epidural space or spinal subarachnoid block. These data can be ascertained only by a properly performed lumbar puncture together with an adequate chemical examination of the cerebrospinal fluid. Signs of meningitis and paralysis resulting from unrecognized compression or destruction of the spinal cord are late manifestations, and their presence is not essential to the diagnosis. Treatment is surgical. It should provide complete and adequate drainage of the abscess if at all possible. The operative wound should be left completely open and without sutures.

[J. A. M. A.]

THE COURSE OF THE TASTE FIBERS AND OTHER AFFERENT TRACTS IN THE THALAMUS. A. ADLER, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:208 (Dec.) 1933.

Adler reports the case of a patient, aged 20, who, besides paralysis of convergence and of accommodation, showed loss of taste on the left side and a sensory disturbance on the left side which was most severe in the face. Necropsy showed a small tumor, 1 cm. in diameter, which had destroyed the central gray matter from the junction of the third ventricle and iter to the large oculomotor cells. A prolongation of the tumor reached into the right side of the thalamus.

The central course of the taste fibers is not clear; they enter the brain stem by the glossopharyngeal and intermediate nerves, and possibly also by the trigeminal and vagus nerves. According to Wallenberg, the fibers which run in the cerebral projection of the tractus solitarius medullae oblongatae unite with the taste fibers from the oral region of the descending trigeminal root. Others consider the nucleus intercalatus as the gathering point of the various taste fibers in the brain stem. Winkler said that the dorsal longitudinal fasciculus, which lies just under the ependyma, conducts taste fibers from the various vegetative centers into the diencephalon. This appears to be disproved by Adler's case, in which both these bundles were destroyed by a tumor, and yet disturbance in taste was unilateral. Adler's case shows that the taste fibers which run to the diencephalon with the secondary trigeminal tract lie on the medial aspect of the thalamus in the immediate vicinity of the ventricle in a small area, so that a focal lesion may cause a severe disturbance of taste. It is impossible to state whether this is part of the secondary tract or whether it represents a diencephalic commutation center.

ALPERS, Philadelphia.

PSYCHOTHERAPY IN PUBLIC MENTAL HOSPITALS. RICHARD H. HUTCHINGS, Am. J. Psychiat. **13**:659 (Nov.) 1933.

The hospital for mental diseases should provide an environment in which the patient has no feeling of responsibility for what goes on; good results cannot be accomplished unless this feeling of relaxation is encouraged. Every effort must be made to make the admission of the patient cheerful. The attendant who escorts the patient should come as a friend and counselor and not as an officer to seize the subject's personal liberty. Show of authority should be made only when opposition develops. The receiving room should be small and homelike; the doctor should come promptly and be prepared to listen patiently. It is not wise to allow the patient to make the transference to a nurse, attendant or other patient before the physician arrives. For this reason it may be well to segregate the newly admitted patient until the formal mental examination can be made. This should be done as soon as possible. The first questions should concern the patient's physical comfort; effort should be made by direct questioning to find what can be done for him. Conversations between patients about their illness must be discouraged. The physician should assume a skeptical but not ridiculing attitude toward delusions and should offer some explanation in line with reality. One must meet the patient on common ground and enter into his infantile attitudes as far as possible and encourage his unrestrained expression. Occupational therapy should be stressed

as a means of exteriorizing the patient and teaching him to cooperate in group activities. Recreations and amusements of every kind are desirable, especially those in which the patients are participants. DAVIDSON, Newark, N. J.

THE RELATION OF THE PREMOTOR CORTEX TO MOTOR ACTIVITY. PAUL C. BUCY, J. Nerv. & Ment. Dis. **79**:621 (June) 1934.

The cerebral cortex exerts its motor effect largely through two principal channels of outflow: the pyramidal tracts arising from the motor area (area 4) and extrapyramidal pathways arising from the premotor area (area 6). In studying the activities of area 6, the following observations have been made in monkeys: 1. Stimulation of area 6 gives rise to: (*a*) isolated sustained responses mediated entirely by pathways to area 4; (*b*) complex contralateral responses effected by paths which pass both to area 4 and to subcortical centers; (*c*) movement in the ipsilateral extremities; (*d*) torsion of the trunk, and (*e*) epileptiform after-discharge, more readily produced than by stimulation of area 4. 2. Extirpation of area 6 results in: (*a*) a deficit in the initiation of purposeful movement; (*b*) awkwardness in complex movement; (*c*) involuntary reflex grasping, and (*d*) appearance of spasticity and certain righting reflexes. 3. Extirpation of areas 4 and 6 bilaterally reduces the animal to the motor status of a thalamic preparation.

The author draws the following conclusions: Areas 4 and 6 constitute the origin of the major motor projection systems of the cortex. Area 6 is primarily concerned with the integration of complex movement. Involuntary movements of the type seen in athetosis and torsion spasm are associated with the activity of area 6. Area 6 exerts direct control over the ipsilateral extremities. Area 6 may be more prone than area 4 to give rise to voluntary seizures of cortical origin. Area 6 exerts an inhibitory influence over the subcortical centers concerned in the postural and righting reflexes. HART, Greenwich, Conn.

ACTION CURRENTS OF THE CENTRAL NERVOUS SYSTEM OF THE FROG. C. UMRATH and K. UMRATH, Arch. f. d. ges. Physiol. **234**:562, 1934.

After the vertebral canal of the frog was opened, one electrode was placed on the dorsal surface of the cord or on the posterior roots and the other electrode on the vertebral canal. The currents were recorded by an oscillograph. A second oscillograph recorded the electromyogram of the muscles of the foot. After the dorsal roots from the eight to the tenth dorsal were severed, the sciatic nerve of the same side was stimulated. An action current was led off from the central stump of the severed posterior roots. The oscillographic record showed that the positive part of this current was more intense than the negative part. It is assumed that this action current is due to the antidromic excitation of the motor neurons. After stimulation of the sciatic nerve or its branches, with the posterior roots intact, negative action currents were recorded from the dorsal surface of the cord. Mechanical stimulation of the toes yielded negative action currents of from 0.4 to 0.7 second's duration on the spinal cord, the medulla oblongata, the mesencephalon and the telencephalon. When rhythmic contractions of the muscles were elicited reflexly by stimulation of the skin with acetic acid, action currents in which the positive current was more intense than the negative current were led off from the dorsal surface of the lumbar segments. The authors assume that these currents originate in intercalated neurons of the cord. E. SPIEGEL, Philadelphia.

THE RETARDED CHILD IN THE RURAL SCHOOL. ANNETTE BENNETT, Ment. Hyg. **17**:466 (July) 1933.

Although the incidence of mental defects in rural districts is almost twice that in the cities, the former are inadequately provided with special facilities for the care of retarded school children. At present, special classes are often provided for these children in centralized township or district schools, but this provision is

unsatisfactory because of the distance from the childrens' homes and because of the heterogeneous mixture of ages and intelligence quotients to be found in these special classes. The social stigma associated with special treatment seems to be more prominent in country districts, a situation which further complicates the problem. If special grouping could be provided within the rural school, it might be possible to accept the retarded children with intelligence quotients above 60 in the ordinary schoolhouse. Bennett believes that the state rather than the school district, township or county should assume the responsibility of caring for the retarded child, because of the necessity for expert guidance and uniform policy. Rural teachers are in need of instruction in the understanding and management of these children. The elaborate equipment and personnel required to make a correct diagnosis and to test, classify and teach defective children properly cannot be provided by rural districts, and an increasing consciousness of the state's responsibility in this field is necessary. Courses in the study of subnormal children should be required in the curricula of normal schools, and postgraduate instruction for rural supervisors and teachers may be necessary at present.

DAVIDSON, Newark, N. J.

FALSE NEUROPTICOMYELITIS, IN REALITY A SYNDROME OF LICHTHEIM. A. MORIEZ, Rev. d'oto-neuro-opht. **12**:271 (April) 1934.

The illness of the patient observed by Moriez had already existed for two years and was in a stage of regression. A woman, aged 39, had had hemophilia and rickets in childhood. Debilitated by helminthiasis and unfavorable climatic conditions that resulted in severe anemia, at the time of a grave obstetric traumatism she became suddenly blind and suffered from flaccid paraplegia with febrile reaction. The paraplegia regressed slowly, leaving an accentuated patellar reflex, periorbital headache and various paresthesias. The amaurosis diminished more rapidly, leaving behind it double optic neuritis, with integrity of the macular fibers. These signs are all habitual in neuro-anemic lesions, and such was the diagnosis in the case reported. The polymorphism of anemic myelitis is known; there are a posterior ataxic, an anterolateral motor and even a cerebellar type. A notable fact was the enlargement of the visual fields after antianemic treatment. Older psychiatrists glimpsed the interdependence of gastric secretion, hematopoietic function and disturbances of nerve conductivity. It seems that a therapy which restores the digestive function has a happy effect also on the coexisting blood picture and on the conductivity of the spinal marrow and nerves.

DENNIS, San Diego, Calif.

MALARIAL MENTAL STATES AND PARALYTIC PARAPHRENIA. PIERRE MASQUIN and JACQUES BOREL, Encéphale **29**:73 (Feb.) 1934.

In the course of the treatment of dementia paralytica by malaria there are often observed disturbed mental states not apparently a part of the original psychotic picture. These may be summarized as paranoid delirium, megalomania, negativism, persecutory ideas, etc., and are together designated "paralytic paraphrenia." They do not seem to be progressive. Certain authors have noted these developments—well along in the course of malarial attacks—and have attributed them to the prolonged infection. These observers, on the contrary, essay to establish the relationship of these disturbances to the modifications of the mental state. That is, they are not side effects of malarial therapy but are indexes of an improving mental status. Evidence for this is found in that they sometimes appear in cases of paralysis in which the condition is improving under other forms of fever therapy. Also, occasionally preexisting psychopathic states appear as the deterioration of the paralytic syndrome is alleviated.

Brief histories of twenty-two patients are included in the article, the wide time variation in the appearance of the secondary mental states being shown.

ANDERSON, Los Angeles.

ACTION POTENTIALS IN SYMPATHETIC NERVES, ELICITED BY STIMULATION OF FROG'S VISCERA. SARAH S. TOWER, J. Physiol. **78**:225 (June 12) 1933.

The action potentials developed in frogs' sympathetic nerves during stimulation of the viscera were studied by means of amplification and photographic recording. These potentials formed a series in which three dominating types could be discerned. Tower calls them fast impulses, slow impulses and waves. The fast impulses represent activity of a mechanism responding to tension rather than to touch. They are elicitable from the mesentery and adjacent peritoneum but not from the hollow viscera or from the parenchyma of organs. The slow impulses represent activity of a mechanism responding to injurious stimulation and of nearly ubiquitous distribution. The reactions of decerebrate frogs to the stimuli evoking this activity are those considered indicative of pain. The waves represent an activity that is more difficult of analysis. Characteristically they are diphasic action potentials of a duration of less than 0.03 second. They reach a maximum during sensory stimulation but appear also in control records. The author tentatively interprets them as synchronized discharges in efferent sympathetic fibers.

ALPERS, Philadelphia.

MODIFICATIONS OF CEREBRAL PLETHYSMOGRAPHY DURING EXCITATION OF THE LABYRINTH. G. MARINESCO, S. DRAGONESCO and A. BRUCH, Rev. d'oto-neuro-opht. **12**:187 (March) 1934.

Following investigations of the vestibulovegetative reflexes, the authors have made plethysmograms of the cerebral contents in two patients with openings in the skull. During the cold caloric test a slight increase of the pulsatile oscillations was found, which was more manifest at the time of the appearance of the nystagmus and vertigo, and a change in the volume of the cerebral mass. Analogous phenomena appeared during galvanic excitation. The hypothesis is that afferent impulses from the labyrinth are transmitted from the bulbopontile vestibular nuclei to the vegetative centers (especially the vasomotor centers) in the bulbar floor; from there the impulses are reflected along the efferent vagosympathetic pathway. The conclusions from these observations are: (1) Labyrinthine excitation produces manifest cerebral vascular reactions; (2) the fact that these reactions follow stimulation by both cold water and galvanism shows that the point of departure of the reactions is the vestibular apparatus.

DENNIS, San Diego, Calif.

THEORIES OF MUSCULAR CONTRACTION. A. D. RITCHIE, J. Physiol. **78**:322 (June 12) 1933.

On the assumption that the first chemical change known to occur in a muscle after stimulation is the breakdown of phosphagen, this reaction may be the causal process producing contraction (chemical theory); or, contraction may be due to liberation of electrical or mechanical potential energy and not to the breakdown of phosphagen. This reaction then would be the first of the recovery processes by which the potential energy is restored (physical theory). On the basis of the physical theory, changing the rate of breakdown of phosphagen should alter the duration of the refractory period in the same sense. On the basis of the chemical theory, it might be expected to alter the duration of the apparent latent period in the same sense, provided other factors remain constant. The rate of breakdown of phosphagen in a muscle poisoned by sodium iodo-acetate can be increased by making the tissue more acid with carbon dioxide and diminished by exhausting the store of nitrogen. Ritchie found that the results of his experiments on the ventricle of the frog's heart are in favor of the physical theory and lend no support to the chemical theory.

ALPERS, Philadelphia.

EPILEPTIC MYOCLONUS. L. MARCHAND, Encéphale **29**:217 (April) 1934.

The symptom complex described by various authors under the general heading of myoclonic epilepsy is reviewed, and a case is presented in great detail. At the

age of 6 a child had an acute illness, which was followed by a tonic spasm of thirty minutes' duration. At the age of 13 he began to have difficulties of speech; at 16, generalized clonic movements developed, and there was progressive intellectual enfeeblement. At 17 there were difficulties in walking and pyramidal signs; at 18, alternate crises of delirium and somnolence. At 21 attacks of decerebrate rigidity developed, leading to cachexia and death at 22. Autopsy showed diffuse sclerosis and degenerative changes in the large cells of the cortex, in the optic tracts, in the locus niger and in the dentate nucleus of the cerebellum. Amyloid and hyaline degenerations were the main types.

An account of the varied anatomicopathologic changes that have been described in many cases is given. Nearly every area in the central nervous system had been incriminated. Especially is it to be noted that investigators have tended to find pathologic changes in areas in which they are themselves most interested.

ANDERSON, Los Angeles.

EXOPHTHALMOS WITH UNILATERAL PREDOMINANCE IN A PATIENT WITH EXOPHTHALMIC GOITER AND NASOPHARYNGEAL TUMOR. H. ROGER, N. CARREGA and M. AUDIER, Rev. d'oto-neuro-opht. **12**:184 (March) 1934.

A patient, aged 39, suffering from goiter, presented a marked predominance of exophthalmos in the right eye associated with a polyp in the right nostril. The question arose as to whether the nasal condition was the cause of the more marked exophthalmos on the same side. The diagnosis of a malignant growth was ruled out on account of the age of the patient, the duration of the process and the reducibility of the exophthalmos. The suggestion is offered that the pathogenesis in this case is a reflex mechanism from irritation of the sympathetic nasal filaments in a subject whose sympathetic nervous system was already sensitized by the presence of exophthalmic goiter. Special attention is drawn to the success of the administration of acetylcholine and yohimbine in controlling the cardiovascular phenomena. Villaret and Justin Besançon have shown that yohimbine acts particularly on the cervical sympathetic nervous system. The addition of acetylcholine adds a hypotensive action to effect.

DENNIS, San Diego, Calif.

VITAMINE THERAPY IN PULMONARY TUBERCULOSIS: V. THE EFFECT OF VIOSTEROL ON THE DIFFUSIBLE AND NON-DIFFUSIBLE CALCIUM OF THE BLOOD AND SPINAL FLUID. PAUL D. CRIMM and J. W. STRAYER, Am. J. M. Sc. **187**:557 (April) 1934.

Crimm and Strayer begin with the assumption that the amount of calcium in the spinal fluid represents the diffusible fraction of calcium in the blood. In ten cases of pulmonary tuberculosis, the normal blood calcium averaged 11.1 mg. and the phosphorus 4.6 mg. per hundred cubic centimeters; following the administration of viosterol, of high potency not obtainable on the market, the serum calcium rose to 15.1 mg., and the phosphorus to 5.2 mg. Similarly, the spinal fluid calcium rose from 6.1 to 7.2 mg., and the phosphorus, from 2.1 to 2.4 mg.; the average diffusibility ratio of 127 per cent dropped to 96 per cent. It is believed that viosterol increases the nondiffusible calcium most markedly. It is concluded that an increase in nondiffusible calcium favors the healing of pulmonary tuberculosis.

MICHAELS, Boston.

THE RELATION OF THE THYROID AND THE HYPOPHYSIS TO THE MOLTING PROCESS IN THE LIZARD, HEMIDACTYLUS BROOKII. G. K. NOBLE and HELEN T. BRADLEY, Biol. Bull. **64**:289 (June) 1933.

Either thyroidectomy or hypophysectomy lengthens the period between molts in the lizard, Hemidactylus Brookii, but neither operation entirely prevents molting. Thyroidectomy does not delay the appearance of the molt immediately following the operation but affects all later molts. Intramuscular injections of thyroxin in

concentration of 1 : 10,000 and later of 1 : 30,000 into thyroidectomized lizards on alternate days bring a return of the molt to its normal periodicity. However, neither injections of thyroxin nor implantations of fresh lizard thyroid increase the frequency of molt in the intact lizard. Completely hypophysectomized Hemidactylus Brookii turns a pale gray and remains this color permanently under varying environmental conditions. Removal of the pars anterior of the pituitary gland alone has the same effect on delaying the molt as removal of the whole gland.

COBB, Boston.

SYMPATHETIC GANGLIONECTOMY FOR GANGRENE DUE TO THROMBO-ANGIITIS OBLITERANS. H. HAMILTON STEWART, Brit. M. J. **1**:100 (Jan. 20) 1934.

Hamilton describes the case of a man, aged 25, a gentile, who had lost both lower limbs from gangrene due to Buerger's disease and who was in imminent danger of losing both upper limbs from the same condition. The inferior cervical and first thoracic ganglia were removed on both sides by an exposure obtained by costotransversectomy at the level of the second rib. Hamilton thinks that the anterior approach is more difficult than the one described, that exposure is often inadequate and that an incomplete operation is likely to result. The explanation of how sympathetic ganglionectomy can improve the blood supply to a limb when the larger arteries are blocked with organizing thrombi seems to be that the smaller arteries are allowed to dilate and the collateral circulation is thereby improved. The results in this case are remarkable, the patient being able to do strenuous work with his upper extremities after the operation was performed.

FERGUSON, Niagara Falls, N. Y.

THE EFFECT OF SYMPATHETIC NERVE STIMULATION ON THE POWER OF CONTRACTION OF SKELETAL MUSCLES. A. B. CORKHILL and O. W. TRIGS, J. Physiol. **78**:161 (May 23) 1933.

Corkhill and Trigs found that when the sympathetic nerves to isolated fatigued skeletal muscles are stimulated there occurs marked recovery in the strength of contraction. The effect is obtained only for indirectly excited contractions but never for the directly excited. It seems, therefore, to be exerted through the end-organs. The results of the authors on these points confirm those of Orbeli. The possibility that this effect is an experimental artefact is excluded. Its occurrence is not dependent on improved blood supply, and the effects of stimulation of the sympathetic nerves may be imitated even in detail by appropriate treatment with epinephrine. The authors believe that the features of this effect can be most readily reconciled with a theory of a hormonal origin, and they discuss the bearing of these observations on the current histologic theory of double innervation.

ALPERS, Philadelphia.

SURGICAL CONSIDERATIONS OF EXOPHTHALMIC GOITER. BREMOND, Rev. d'oto-neuro-opht. **12**:126 (Feb.) 1934.

Exophthalmic goiter is defined as a tumorous hypertrophy of the thyroid body to which is added a secretory disturbance due to hyperfunction and deviation. The tumor of the thyroid always occurs first, and as soon as the secretoglandular disorders develop signs of involvement of the neurovegetative system appear. The distinction between exophthalmic goiter and dysthyroidism and toxic adenoma is not justified. The state of the pulse is an index of operability; if it exceeds 120 the patient should be put to rest. If it is over 130 the thyroid arteries are ligated after amelioration has been obtained. Complications of the operation are rare. With the necessary precautions and the proper selection of cases, the operative mortality should be practically nil. Complete cure ought to be obtained in from 36 to 40 per cent of cases.

DENNIS, San Diego, Calif.

THE ENCEPHALIC CONTROL OF TONE IN THE MUSCULATURE OF THE URINARY BLADDER. OTHELLO R. LANGWORTHY and LAWRENCE C. KOLB, Brain **56**:371 (Dec.) 1933.

Experiments were performed on thirty-three adult female cats in which a quantitative method for measurement of increased tone in the bladder was utilized. After decerebration through the optic colliculi, the bladder emptied on as little as one fourteenth of the volume of fluid required to produce reflex micturition in the intact, anesthetized preparation. The observations of Barrington are confirmed. When the transection is made below the acoustic colliculi, reflex micturition is abolished and the bladder shows retention with overflow. In the upper portion of the hindbrain there is a mechanism controlling tone in the smooth musculature of the bladder similar to the reflexes localized in the same region which control tone in the striated muscles of the extremities. MICHAELS, Boston.

TUMOR OF THE FOURTH VENTRICLE. J. A. BARRE and E. WORINGER, Encéphale **29**:289 (May) 1934.

A case is described in detail in which necropsy disclosed a fibrillary astrocytoma, partially cystic, taking origin from the floor of the fourth ventricle. Then follows a general classification of tumors of the fourth ventricle: (1) a general form, yielding symptoms based on pressure in the angles and floor of the ventricle; (2) a lateral angle form; (3) a superior angle form, with spontaneous vertigo, transitory in character, and without induced vertigo or vomiting; (4) an inferior angle form (described in the case presented), and (5) a vermis form, evolving above and behind the cerebellar vermis and making pressure on it.

ANDERSON, Los Angeles.

COLOBOMA OF THE OPTIC NERVE ASSOCIATED WITH POSTERIOR LENTICONUS. JAMES S. SHIPMAN, Arch. Ophth. **11**:503 (March) 1934.

This paper is in the nature of an ophthalmologic review, dealing with coloboma of the optic nerve as a rather rare congenital anomaly, especially when it is unassociated with defects of the surrounding choroid. Vossius, Caspar and Saemisch first started a search of the literature for these cases. Coates, in 1907, added reports of six cases, in all of which microscopic studies had been made. Since that time others have considered the subject, the last report being by Calhoun in 1930, a paper which appeared in the *Archives of Ophthalmology* (**3**:71 [Jan.] 1930). The present article is illustrated with satisfactory photographs of the fundus.

SPAETH, Philadelphia.

THE CURE OF OZENA BY SUPPRESSION OF THE NASAL RESPIRATION. D. I. VASILIU and CRISEOTA, Rev. d'oto-neuro-opht. **12**:276 (April) 1934.

A patient, aged 24, who had suffered from ozena since infancy, complained of embarrassed respiration from papillomatosis of the larynx, and a tracheotomy was performed. In spite of the fact that no treatment of the nose was undertaken, the ozena disappeared, and the patient remained free from symptoms for eight months. Ten other patients with typical ozena were treated by occlusion of one nostril. After forty-eight hours the nasal plug was removed; the occluded side was found to be free from crusts, while in the other side the crusts were as abundant as ever. Owing to irritation from the occluding plugs, it was not feasible to keep them in place longer than forty-eight hours. The crusting soon recurred.

DENNIS, San Diego, Calif.

THE REFLEXES OF WINKING AT A THREATENING OBJECT. G. G. J. RADEMAKER and RAYMOND GARCIN, Encéphale **29**:1 (Jan.) 1934.

This study indicates that a lesion of the rolandic or occipitorolanic cortex can abolish the reflex of winking at a menacing phenomenon in the temporal field of

the side opposite to the lesion, and that this occurs in the absence of total hemianopia. This is of interest not only for the study of the conduction tracts of the different reflexes but also for neurologic diagnostic purposes. Confirmatory findings have been reported. There seems to be a center for that part of the seventh nerve going to the orbicularis palpebrarum muscle in the cortex of the rolandic occipital area of the opposite side, injury of which is responsible for loss of the reflex.

ANDERSON, Los Angeles.

THE DIFFERING EFFECTS OF DIFFERENT PARTS OF THE VISUAL FIELD UPON THE CHROMATOPHORE RESPONSE OF FISHES. FRANCIS B. SUMNER, Biol. Bull. **65**:266 (Oct.) 1933.

Darkening the lower half of the field of vision by the insertion of false corneas of pyroxylin (celloidin) resulted in pronounced darkening of the entire dorsal surface of the fish (Fundulus parvipinnis), even when the animal was kept on a white background. In experiments during the winter and early spring it was found that transparent "corneas" which were stained yellow, either throughout their entire extent or in the lower half only, led to the assumption of a distinctly yellowish hue by the fish.

COBB, Boston.

THE TREATMENT OF TETANUS IN THE HOSPITALS OF LANCASTER, PA., OVER A PERIOD OF 30 YEARS. ANNA P. KLEMMER and EDWARD S. CROSLAND, Am. J. M. Sc. **187**:700 (May) 1934.

Of ninety-six patients with tetanus, those (nineteen) who received serum intraspinally in conjunction with any other route of administration showed a mortality of 68 per cent, although the total mortality for all patients, including the eleven who did not receive antitoxin, was only 58 per cent. Tetanus as a sequel to vaccination occurred in 10.4 per cent of the cases. The most common wound of entrance was the "splinter" (13 per cent). The highest mortality rate was found in patients in whom tetanus developed between the fifth and the tenth day after injury.

MICHAELS, Boston.

CONCERNING THE PSYCHIATRIC SEMEIOLOGY. C. ENDERLE, Arch. gen. di neurol., psichiat. e psicoanal. **15**:5, 1934.

After having studied the evolution undergone by psychiatric semeiology in relation to the changes of theories of the genesis and the interpretation of mental symptoms, the author discusses the theoretical foundation and practical applications of the psychiatric semeiology of the school of de Sanctis. He concludes that the study of the total personality of a patient with mental disease must be carried along with an active study of the "bedside semeiology" supported by an exact "laboratory semeiology."

YAKOVLEV, Palmer, Mass.

SYSTEMATIC DENIAL OF DEATH. H. BEAUDOUIN and R. BRIAN, Encéphale **29**:306 (May) 1934.

An interesting series of case histories is presented showing an unmindfulness or unwareness on the part of the patient of the fact of death. It does not seem to be a particularly uncommon manifestation in certain psychotic states. The denial was in some instances merely a part of a generalized doubt or negation of many or all objective facts; in some it was a refusal to apprehend the immediate fact of death of a close relative; in still others it was a gradual retrospective negation of a previously apprehended fact.

ANDERSON, Los Angeles.

THE EFFECT OF UNILATERAL SECTION OF THE PERONEAL NERVE OF THE ALBINO RAT ON THE NUMBER OF MYELINATED FIBERS IN THE INTACT NERVE OF THE OPPOSITE SIDE. K. TAMAKI, Anat. Rec. **56**:219 (June 25) 1933.

Section of the peroneal nerve of one side produces changes in the contralateral nerve, expressed as a loss of fibers or a retardation in their production with age.

The fibers so affected are thought to be myelinated branches of the main fibers forming the nerve. It seems probable that these changes induced in the contralateral nerve are due to humoral stimuli represented by substances arising in the damaged neurons of the sectioned nerve.

COBB, Boston.

CALCIUM THIOSULPHATE IN THE TREATMENT OF THE COMPLICATIONS OF NEOARSPHENAMINE AND BISMUTH ADMINISTRATION IN SYPHILIS. A. E. W. McLACHLAN, Brit. M. J. **1**:916 (May 27) 1933.

The results of treatment with calcium thiosulphate in six cases of intolerance to neoarsphenamine or bismuth are reported. In these cases the drug appeared to exert a definite curative influence. The usual procedure was an intravenous injection of 0.6 Gm., administered daily for three days, then biweekly.

FERGUSON, Niagara Falls, N. Y.

HYPERMOBILITY OF JOINTS WITH SUPERIMPOSED POSTENCEPHALITIC PARKINSONISM. JOSEPH J. MICHAELS and OLIVE M. SEARLE, J. Nerv. & Ment. Dis. **77**:246 (March) 1933.

A young man, aged 20, whose heredity showed allergy, had congenital hypermobility of the joints, on which was superimposed encephalitis with the sequelae of hypertonus of the muscles. Other findings were eosinophilia, increased bleeding time and a hyperbilirubinemia.

HART, Greenwich, Conn.

PATHOLOGY OF MYATONIA CONGENITA. SIDNEY KAHR, Arb. a. d. Neurol. Inst. a. d. Wien. Univ. **35**:29, 1933.

A review of the literature and personal investigation of the clinico-anatomic features in a case of myatonia congenita lead Kahr to believe that the disease is not to be included among the congenital heredodegenerative diseases. He is inclined to attribute the condition to exogenous factors in fetal life which produce pathologic changes of a heredodegenerative character. The author presents no data as to the possible nature of these exogenous factors.

KESCHNER, New York.

HUMAN BRACHIAL PLEXUS UNITED INTO A SINGLE CORD. DESCRIPTION AND INTERPRETATION. EDWARD SINGER, Anat. Rec. **55**:411 (March 25) 1933.

An anomaly of the axillary artery was associated with an irregularity of the brachial plexus. There was a gross anomaly in the union of all its cords and divisions. The abnormality of the plexus lies only in its extraordinary form. The anomaly was found to have no bearing on the function of the arm, as confirmed by the hospital report.

COBB, Boston.

THE VOLUME AND SIZE OF THE SURFACE OF THE AREA STRIATA IN MAN. EDITH GERHARDT and HANS KREHT, J. f. Psychol. u. Neurol. **45**:220, 1933.

The authors undertook a detailed investigation of the measurements of the volume and surface of the right and left areae striatae in man. They found a difference of a little more than 1 per cent in volume between the two sides, which they attribute to technical errors. They believe, therefore, that in man the areae striatae are equal in volume and surface.

KESCHNER, New York.

CIRCUMCISION AND SYPHILIS. V. E. LLOYD and N. L. LLOYD, Brit. M. J. **1**:144 (Jan. 27) 1934.

The results of the analysis reported indicate that the absence of the prepuce is not such an important preventive factor against the acquisition of syphilis as is

commonly believed. Circumcision was noted a little more frequently in cases of gonorrhea than in those of syphilis and a little less frequently in the nonvenereal group.

FERGUSON, Niagara Falls, N. Y.

A PROCEDURE FOR DECEREBRATING THE RAT BY THE ANEMIA METHOD. W. F. WINDLE and W. L. MINEAR, Anat. Rec. **57**:1 (Aug. 25) 1933.

The method reported here is essentially a modification of that of Pollock and Davis (1924), who developed the technic of producing the decerebrate state in the cat by ligating the carotid and basilar arteries. One cannot easily reach the basilar artery from the mouth of the rat; therefore, the authors use a cervical, transpharyngeal approach.

COBB, Boston.

OBSERVATIONS ON THE DIAGNOSIS OF SPINAL BLOCK BY MEANS OF LIPIODOL. H. H. MOLL, J. Neurol. & Psychopath. **13**:14 (July) 1932.

The intracisternal injection of iodized poppy-seed oil 40 per cent is a safe and valuable procedure, with a proper technic, for determining the site of a spinal block. Cases with untoward symptoms resulting therefrom are infrequent. The technic of intracisternal injection is described, and the results are interpreted with appropriate roentgen illustrations.

SPERLING, Philadelphia.

SURGICAL RELIEF OF THE HEADACHE OF MIGRAINE. D. G. DICKERSON, J. Nerv. & Ment. Dis. **77**:42 (Jan.) 1933.

The symptomatology of migraine is reviewed, and the theory of arterial spasm in the cerebral arteries offered by Bramwell is discussed. Dickerson cites seven cases with operative treatment at the Swedish Hospital, Seattle, in which ligation of the middle meningeal artery relieved the pain entirely.

HART, Greenwich, Conn.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Oct. 26, 1934

D. J. McCarthy, M.D., *President, in the Chair*

Pick's (or Alzheimer's) Disease. Dr. Alfred Gordon.

Pick's disease is a form of precocious mental deterioration, diagnosis of which can rarely be made with certainty during life. During the development of the dementia there may be observed disorientation, disturbance of behavior and activity, defect of esthetic and moral senses and of criticism and affectivity, and incoherence. In the course of the progress of the disorder, Pick observed aphasic or apraxic phenomena in some cases and stereotypy, perseveration, taciturnity or mutism, akinesia, disturbance of gait, paretic phenomena and contractures in others.

A patient, aged 58, first came under observation about twelve years ago. At that time he presented psychoneurotic manifestations, chiefly of a hypochondriac character. One year later he had several periods of cyclothymic phenomena. At times he was mildly depressed, and at others he was very talkative and somewhat exalted. He also suffered from persistent insomnia. In 1924 he first exhibited signs of the condition from which he is suffering at present in an advanced form. He became apathetic and indolent and began to lose interest in every one and everything. He was married and had several children to whom he was formerly much attached. They no longer interested him, and only occasionally would he inquire about them. The same attitude was evident toward his wife. The wife and children soon left him, without ill feeling on his part. He apparently began to lose all conception of obligations or of ethical standards. However, when pressed with regard to his family and relatives, the apathy and indifference left him momentarily; he would brighten up and say quickly, "It is too bad," and then return promptly to his former state. Memory for past and recent events remained intact for a long time.

About a year ago he began to show peculiarities of gait. He walked very slowly at first. There was no rigidity in the extremities, but they presented some resistance to passive movement. At about the same time paresis of the right arm and leg developed, with some impairment of speech. This occurred without loss of consciousness. The condition continued to progress.

At present the gait is slow. The patient walks with small steps, but there is no hemiplegia. At the last examination the knee jerks were exaggerated, and there was no Babinski sign. The right upper extremity was somewhat weak, but there was no rigidity. Speech was indistinct and thick; there was no anarthria or sensory aphasia. Further somatic examination gave entirely negative results. The sensations, pupils, eyegrounds and cranial nerves were normal. Studies of the basal metabolism, the blood cytology and the blood chemistry gave negative results. The Wassermann reaction of the blood and of the spinal fluid was negative. Examination of the ears, nose, throat and teeth and of the genito-urinary tract and the cardiovascular system showed no special deviations from the normal. From a mental and emotional angle the patient is very quarrelsome; he shows some paranoid trends and finds fault with every one. He suspects every one of harboring bad intentions toward him. He is talkative and repeats the same stories over and over. At times he exhibits stereotyped movements, repeating the same act several times. At times he is hyperactive. He eats voraciously but very carelessly, allowing food to run out of his mouth without attempting to wipe it away. He is

becoming more and more unclean about himself and urinates and defecates in his clothes and in bed. He must be forced to wash and bathe. He does not change his clothes until forced to do so. His social attitude and ethical views are not normal. He is totally oblivious of, and indifferent to, social obligations. He gives no thought to his family, and when reminded says that he does not care what becomes of them. He does not know where they live and does not inquire of their whereabouts. He is not interested in topics of the day, in community life or in national affairs. He does not care to read newspapers. He spends his days in quarreling with others and waits eagerly for something to eat. At times he is in a state of hebetude, and then again he will awaken and resume his mannerisms and his annoying and disturbing attitude toward all. Poverty of emotion and intellect is gradually becoming more pronounced. What is particularly striking is that in the midst of progressing dementia the memory is preserved to a great extent. Lately, however, there have been strong indications of some failure in recalling facts of a familiar nature. The aphasic disorder is becoming more pronounced and walking more difficult. The patient is evidently approaching a terminal stage of deterioration and dementia.

Although Pick's and Alzheimer's syndromes present somewhat different clinical pictures, they are essentially analogous, if not similar, pathologic entities by virtue of the diffuse atrophic changes in the brain. Predominance of involvement of certain cortical areas will give rise to the manifestations observed in either one or the other of the two conditions. Since presenile mental deterioration develops insidiously and progressively without the presence of arteriosclerotic changes in the brain, a premature selective involution of the neurons is in all probability the chief cause. It suggests an abiotrophic anomaly, perhaps of hereditary and degenerative character.

DISCUSSION

DR. ROBERT MATTHEWS: Dr. Hoedemaker and I reported a case thought to be an instance of Pick's disease in December 1932. At that time we thought that it was the first case reported in the English language. However, a case was reported in the *Journal of Mental Science* in June 1932, with which we were not familiar. Since, Thompson and Kahn have reported 2 cases and another was reported by Nichols before the Boston Society of Neurology.

As regards retention of memory, I believe that memory was affected in practically all the cases cited, although Kahn and Thompson reported that what might be called "ethical memory loss" was first noted. It was a loss of memory that had to do with things of a more or less useful nature. The patients would forget engagements which they had formerly been careful to remember. It was stressed that there was usually a more or less senseless activity or restlessness. The patients, as a rule, moved about with no apparent aim in view. Our patient has shown that symptom to a marked degree. One patient who is still living shows senseless motor activity. She wanders about the ward and has apparently no aim in anything she does. Her memory is entirely gone. She has reached a point of complete dementia, which is the natural outcome in all these cases.

The length of life in Dr. Gordon's case is of interest; the longest period reported is thirteen years. Most patients have died within four or five years after the onset of the illness. The motor phenomenon certainly is not a constant feature. Seldom is there any definite mental trend. Delusions and hallucinations are rarely present.

DR. B. J. ALPERS: I have examined the patient of Dr. Matthews and Dr. Hoedemaker. As far as I know, it is the first instance in which a clinical diagnosis of Pick's disease has been made and confirmed at autopsy. Study of the brain reveals the changes characteristic of Pick's lobar atrophy, the greatest cell loss in the cortex occurring in the three upper layers.

DR. ALFRED GORDON: The striking features in this case are: gradual mental deterioration, increasing emotional poverty, preservation of memory and absence of arteriosclerosis in a man under 60. At no time were there delusions or hallucinations. The condition is distinctly presenile dementia.

APIOL POLYNEURITIS: REPORT OF A CASE. DR. ROBERT DENISON (by invitation) and DR. J. C. YASKIN.

This article will appear in full in the *The Journal of the American Medical Association.*

THE MARCUS GUNN PHENOMENON: REPORT OF A CASE (MOTION PICTURES). DR. FRANCIS C. GRANT.

This case is reported because of the rarity of the symptoms and because operation was successfully performed in a case of this sort for the first time, with complete relief to the patient.

N. R., a man aged 21, was admitted to the Graduate Hospital April 2, 1934, complaining of slight ptosis of the right eyelid complicated by abrupt elevation of the right upper lid on movement of the jaw to the left.

Neurologic examination gave entirely negative results except for the right eye and the associated movement of the jaw and the right upper lid. The following description is a short digest of the results of examinations made by Dr. Bernard J. Alpers, Dr. E. B. Spaeth and myself.

The left eye was normal in all details. With the face at rest there was a moderate degree of ptosis of the right upper eyelid, this lid standing at a level of between 2 and 3 mm. lower than the left lid. Voluntary elevation of the right eyelid was equal to that of the left. The right pupil was round and central. At times both pupils were equal in size and somewhat dilated, but for the most part the right pupil was slightly smaller than the left. There was enophthalmos of the right eye of 1 mm. as compared with the left. Stimulation with a bright light produced an equal contraction of the pupils on the two sides. In accommodation convergence the right pupil seemed to contract to a somewhat less extent than the left. There was some dissociation of movements of the eyeball. On looking to the right the right eye looked straight ahead when the left was at the inner canthus. From this point the right eye moved alone to the outer canthus. This seems to indicate interference with the normal movements of the right eye to the right. Other conjugate movements of the eyes seemed to be entirely normal. There was no ciliospinal reflex response in the right eye. Firm contraction bilaterally of the masseter and temporal muscles, as in the act of chewing, and movement of the lower jaw to the right were followed by no movement of the lid on either side. Movement of the jaw to the left, whether done slowly or rapidly, was followed promptly by an abrupt elevation of the right eyelid so that at least 3 mm. of the sclera was visible above the eyeball. These movements of the right eyelid on movement of the jaw to the left were increased when the patient looked down. The upward movement of the right eyelid on movement of the jaw was not accompanied by any movement of the eyeball or of any of the muscles of the face.

A 4 per cent solution of cocaine instilled into each eye produced greater dilatation on the left side than on the right and reduced slightly the ptosis of the right lid. A 10 per cent solution instilled into the right eye alone equalized the dilatations of the pupils. A 1 per cent solution of homatropine instilled into the eyes caused wide and equal dilatation of both pupils without increasing the ptosis. Most striking was the fact that following the instillation of homatropine movements of the jaw to the left did not result in elevation of the lid. This is my observation, and I am certain of it because I had come prepared to take photographs of the boy, but the presence of the homatropine prevented the spasm and made any attempt to photograph him useless.

It was apparent that elevation of the eyelid accompanied only movement of the lower jaw to the left. If this movement could be prevented it seemed probable that the spasm of the lid could be prevented. With the end in view of paralyzing the motor part of the fifth nerve on the right side, an injection of procaine hydrochloride was instilled into the third division of the nerve. The usual anesthesia of the lower lip and tongue was produced, indicating a successful temporary block

of the nerve. Following this injection the ptosis of the right eyelid increased; voluntary elevation of the right eyelid was difficult, and it could not be raised above the level of the pupil. When the patient opened his mouth the jaw deviated to the right. It was impossible for him to move his jaw to the left, and there was no spasm of the right eyelid on any movement of the face. There was no other facial weakness than the inability to raise the right eyelid. By the end of twenty-four hours, anesthesia of the lip had disappeared. The ptosis of the eyelid had decreased to its original level, and the movement of the jaw to the left would induce the spasm of the lid on the right.

I then suggested to the patient that since the result described had been produced by injecting procaine hydrochloride into the third division of the fifth nerve, we could probably give him temporary relief from the spasm of the lid at the cost of increased ptosis of the right lid by injecting alcohol in the same manner. Twenty-four hours later I made a successful injection of alcohol, using 0.75 cc. of absolute alcohol. The usual anesthesia of the lower lip and tongue was produced. However, there was no increase of the ptosis. Movements of the jaw to the right were free. The jaw deviated to the right on opening the mouth, but the patient could still move the jaw to the left roughly ¼ inch (0.64 cm.), and the usual spasm of the lid accompanied this abortive movement of the lower jaw to the left. It seemed as though the alcohol had not diffused as far as had the procaine hydrochloride and had not picked up all the fibers in the right motor root supplying the right pterygoid muscle. Following this rather surprising and disappointing result, under anesthesia with ether and procaine hydrochloride the motor root was divided intracranially by the temporal approach. No difficulty was encountered until the sensory root was about to be exposed. It was then found that the dura over the posterior edge of the ganglion was adherent, and when the subarachnoid space was entered the sensory root was found to be glued together tightly in one mass instead of floating as more or less individual fibers in the cerebrospinal fluid. In spite of careful search I was unable to distinguish between the sensory and the motor root. I was unwilling to sacrifice the sensory root and satisfied myself with cutting the third division together with part of the ganglion that supplied the third division, trusting that by this maneuver the motor root would be cut as well. After complete hemostasis, the wound was closed as usual.

Following this procedure ptosis of the eyelid was complete. Movement of the jaw to the left was impossible, and no spasm of the eyelid accompanied even passive movement of the jaw to the left. All movements of the right eye at that time were normal. Unfortunately, just before examination and prior to operation in the morning, the boy had been given morphine so that both pupils were somewhat contracted equally. At 2 a. m. on the next day the left side had become spastic and by 4 the patient was comatose. At 6 the wound was reopened and a large postoperative clot was evacuated. After a stormy postoperative convalescence, the patient recovered. After evacuation of the clot, examination showed complete paralysis of the third nerve. Five days after operation weakness of the right side of the face was noted; it progressed to complete paralysis on the eighth day.

The patient was discharged on April 21, when the oculomotor and facial paralysis was complete. The paralysis of the motor part of the fifth nerve and anesthesia resulting from section of the third division of the fifth nerve were still complete. He was seen on June 11 when the facial paralysis had entirely disappeared and the oculomotor paralysis had practically disappeared. Paralysis of the motor part of the fifth nerve on the right and anesthesia in the third division were complete. There was a little more ptosis of the right eyelid than when I first saw the patient. Furthermore, if he made a determined effort to move the jaw to the left and at the same time wrinkled the left side of the face, the right eyelid was still raised; but on normal, natural movements of the jaw there was no movement of the eyelid. The patient was wearing dark glasses and still complained of diplopia, but other than this he seemed to be recovering satisfactorily. He was satisfied with his condition.

By July 20 the diplopia had practically disappeared. I could not find any abnormality in the ocular movements in any plane. Some sensation in the tongue was returning, and the anesthetic area in the face apparently was decreasing in size. The patient could not move the jaw to the left, and there was only an occasional twitch of the right eyelid.

DISCUSSION

DR. WILLIAM G. SPILLER: Dr. Grant's paper is especially valuable because of the surgical treatment with ultimate success. I do not know of a similar case. My attention to the "jaw-winking phenomenon" was first arrested by the paper of W. G. Sym in the *Review of Neurology and Psychiatry* in 1908; this paper was considered by me in a review of the literature in *Progressive Medicine* for that year.

Sinclair, in the *Ophthalmic Review,* October 1895, described three series of movements of the jaw associated with elevation of the upper lid: (1) those in which either lateral movement or wide opening of the mouth causes an elevation of the eyebrow; (2) those in which depression of the lower jaw brings on the elevation, and (3) those in which lateral movement of the jaw alone, as in the process of chewing, sets up the contraction but vertical movements do not. The phenomenon seems to be always unilateral, and ptosis is not invariably present. Dr. Grant's case belongs to the third series.

The first case presenting this phenomenon was described by Marcus Gunn in 1883, and a committee of the Ophthalmological Society, appointed to study the phenomenon, reported that in such cases the levator of the upper lid receives nerve impulses from both the third and the fifth nerve. Those from the fifth nerve are "intended for" the external pterygoid or the digastric muscle, and when one of these muscles is put strongly in action the levator is unintentionally innervated. Harman attempted to trace this associated movement to fishes, but Sym pronounced his conclusions as not convincing.

In Dr. Grant's case there seems to be slight sympathetic deficiency as shown by the usually slightly smaller right pupil, the enophthalmos of the right eyeball of 1 mm. and the necessity of a stronger solution of cocaine to dilate the right pupil to the size of the left. The phenomenon in his case was more pronounced when the patient was looking down. In a few cases it occurred only when the patient was looking down.

Dr. Grant spoke of abnormalities in the associated movements of his patient in looking to the right. Such abnormalities were excessive in a case reported by me in 1927. Homatropine (1 per cent solution) placed in the eyes caused wide dilatation of both pupils. This must have been due to paralysis of the third nerve supply to the iris, but it did not increase the ptosis of the right eyelid and yet after the instillation movement of the jaw to the left did not result in elevation of the right lid. It seems from this that the homatropine in some way paralyzed the abnormal association of the fibers of the fifth nerve to the levator of the right lid.

Procaine hydrochloride injected into the third division of the fifth nerve on the right side caused increased ptosis of the right eyelid; voluntary elevation of the right lid was difficult and imperfect. The effect on the right pupil was not recorded. It seems that the procaine hydrochloride by diffusion affected the cervical sympathetic fibers and through the carotid plexus paralyzed the Müller fibers of the upper lid. I have consulted Dr. A. N. Richards as to this possibility and he writes me: "You may be assured that if the procaine in adequate concentration came in contact with the sympathetic fibers supplying the fibers of Müller, paralysis would result."

When injection of alcohol was used probably the ocular sympathetic fibers were not affected, especially as the motor supply of the right external pterygoid nerve was not completely paralyzed, as it had been by the procaine hydrochloride, indicating that the alcohol had not completely paralyzed the motor root.

It is interesting that on June 11, after the intracranial operation, if the boy made determined effort to move the jaw to the left the right eyelid was elevated,

although he could not move the jaw to the left, as shown by the examination of July 20. He was able to innervate the center for contraction of the right external pterygoid nerve, but only those abnormal fibers from this center to the right levator nerve were capable of responding, as the path to the right external pterygoid nerve was blocked. The operation performed in this case would be useless when the elevation of the lid follows opening of the mouth.

DR. FRANCIS C. GRANT: It seems that the suggestion that Dr. Spiller has made, involvement of the cortical center rather than of any nucleus or peripheral nerve, is a much more likely explanation for this curious movement than anything else I have seen.

PALPEBROMANDIBULAR REFLEX IN FACIAL DIPLEGIA. DR. A. M. ORNSTEEN.

This article will be published elsewhere.

HYPERTROPHY OF THE SUBFLAVOUS LIGAMENT AS A CAUSE OF COMPRESSION OF THE SPINAL CORD. DR. HELENA E. RIGGS.

In 1931, E. B. Towne and F. L. Reichert reported 2 cases of compression of the cauda equina due to hypertrophy of the subflavous ligament (*Ann. Surg.* **94**:327 [Sept.] 1931). I shall add 3 cases, 2 of my own and 1 from the French literature.

My first case is taken from the service of Dr. J. W. McConnell at the Philadelphia General Hospital. The case was reported before the Philadelphia Neurological Society in May 1928, as one of compression of the cauda equina by an extradural band. Not until the publication of the article of Towne and Reichert was it realized that the case was one of compression of the spinal cord by hypertrophied ligamentum flavum. The patient's condition began acutely, one year before admission, with pain in the sciatic distribution of the left leg which was intense, lancinating and almost continuous. An operation on the peripheral part of the sciatic nerve had given no relief. Eight months later the right leg was similarly affected. There was no history of any trauma. Neurologic examination on admission showed weakness of the muscles of dorsiflexion and atrophy, especially of the muscles of the calves. The patellar reflexes were present and equal, and the achilles tendon reflex was absent on both sides; there were no abnormal reflexes. The sense of position and of vibration was lost in both feet. The sense of touch was lost on the posterior portion of the left leg and impaired over the entire right leg. The pain and temperature senses were impaired in both legs, but more on the left. There was no loss of sphincter control. Laminectomy was performed, and an extradural fibrous band was found constricting the cord at the level of the fifth lumbar vertebra. This was 0.5 cm. in diameter, definitely marginated, smooth on the under surface and not adherent to the dura. When the band was cut through, the dural sac below filled and the cauda equina roots spread out. Microscopically, the tissue was similar to that in the previous cases of Towne and Reichert. The patient was relieved from pain six hours after the operation; he was able to return to work in six weeks.

In the second case the history was difficult to secure because of the low mentality and foreign extraction of the patient. There had been a trophic ulcer of the left foot for five years, associated with weakness of the left leg. At the onset there had been pain in the left calf and thigh with difficulty in moving the toes of that foot. There was also difficulty of urination. Examination on admission showed loss of flexion and extension of the left foot, with atrophy of the muscles below the knee. The cremasteric reflex was absent on the left and diminished on the right. Both knee jerks were equally diminished, and the achilles tendon reflex was lost on the left and greatly diminished on the right. No abnormal reflexes were obtained. There was relaxation of the urinary sphincter, with incontinence. Pain sense was lost over the left calf and diminished over the dorsum of the foot and leg. Vibration was lost over the left foot and diminished on the right. Position sense was lost on the left and uncertain on the right. There was perineal and perianal

anesthesia. Iodized poppy-seed oil 4 per cent revealed a block at the level of the third and fourth lumbar vertebrae. On laminectomy an extradural band of yellow, gristly material was found surrounding the posterior portion of the cord at the level of the first sacral vertebra. This was removed, and the dura was opened. Arachnoidal adhesions were found from the second to the lower edge of the third lumbar transverse process and broken up. The diagnosis from study of the excised tissue was the same as in the other cases. The patient improved somewhat after operation but died two months later of meningitis.

The third case was reported by M. A. Flores of Lisbon, Portugal (*Rev. neurol.*, vol. 39, 1923). This is the only case in which there was any history of associated trauma. At the age of 30 the patient was struck across the lumbar region. There were extensive bruises and severe pain for several weeks. One year later there was weakness in the left foot and leg.

Neurologic examination three years after the onset showed diminution of power in the left leg with flaccidity and atrophy and a hyperactive patellar reflex and patellar and ankle clonus on the left. There was a Babinski sign on the left. The reflexes on the right were normal. There was no sensory disturbance, objective pain or loss of sphincter control. Lumbar puncture was performed for the third time in the course of the illness, with negative results. Two days later there was severe continuous pain at the level of the third lumbar vertebra. This progressed down the unaffected leg. There was less severe pain in the paretic limb. This continued for three days, during which there were no objective sensory disturbances. At operation a healed fracture of the laminae of the eleventh and twelfth dorsal vertebrae was discovered. On removing the laminae a thick band of fibrous tissue was found stretching from the middle of the eleventh dorsal vertebra to the edge of the twelfth dorsal vertebra. This band was rough on the outer surface and encircled and compressed the dura and the cord. It was not attached to the dura. When the band was removed the cord was released and returned to normal. The tissue histologically was hypertrophied subflavous ligament. The patient made a complete recovery. The author considered that the callus formed in the healing of the fractured laminae caused adhesions between the subflavous ligaments and the laminae and so brought about the hypertrophy of the ligament.

Comment.—I have discussed 5 cases in which hypertrophy of the subflavous ligaments have caused compression of the spinal cord or of its roots. In only one case did trauma constitute an etiologic factor. In four cases the hypertrophied ligaments were attached to the lower lumbar and sacral vertebrae, thus compressing only the cauda equina, but it is possible that the hypertrophy may occur in the thoracic region and compress the cord itself, as in Flores' case. Analysis of the symptom complex in the 4 cases which involved the cauda equina shows that pain in the sciatic distribution of one side is usually the initial symptom. This is rapidly followed by weakness and atrophy of the leg. The symptoms are slowly progressive, and sooner or later similar symptoms are established on the opposite side. Sensory signs of varying degree are noted in all 4 cases. Following bilateral involvement, symptoms referable to the bladder appear. If the condition is recognized early and an operation is done, complete cure results. If the condition is of long standing the presence of extensive arachnoidal adhesions, as in my second case, may complicate the picture and prevent complete cure. In the one case in which there was pressure on the cord itself, the symptoms were those of involvement of the anterior roots and irritation of the motor tract of one side. Sensory change and involvement of the bladder were not present. Spontaneous pain occurred very late in the condition.

DISCUSSION

DR. J. W. MCCONNELL: My predecessor at the Philadelphia Hospital discharged the patient in case 1 because there was great improvement in the unilateral symptoms. When the man returned to my service six months later, he had not only the original symptoms but on the other side had definite paralysis without much pain. The symptoms increased. An operation gave him quick relief.

IS THERE A "MORAL CENTER" IN THE BRAIN? Dr. N. S. YAWGER.

While reviewing a book on nervous children my attention was drawn to this surprising statement by Cameron: "The delinquent is made, not born. The term moral imbecile is unmeaning and misleading and should be abandoned . . . there is no such thing as a child of high intelligence who, on the point of morals only, is imbecile." Barr said: "Now in amoral imbecility there is a partial or absolute absence of moral sense often as complete as in the absence of sight in the blind. This may not necessarily be associated with physical or mental defect, but it constitutes a defect of its own. . . ."

A thumb-nail sketch of a few personalities bearing on intelligence, emotion and morals may not be amiss. Among the "idiot savants" was "blind Tom," a colored musician whose talent was decided. He became famous and made many concerts throughout America and Europe. He was born a slave and when 7 years of age the family of his master, hearing strange music, found him at the piano. He could at once reproduce the tunes he heard and repeat them after long intervals. Some of his music was from the classics, and if it had been played nervously when first heard, that, too, was included in his rendering. "Blind Tom" could play a different tune with each hand at the same time, yet he was so foolish he would arise and with his audience applaud his own accomplishments. His mental age was 4 years.

Jesse Pomeroy of Massachusetts perhaps spent more time—about forty years—in solitary confinement than has any other prisoner in this country. His crimes began at the age of 13 years, and at 14 he was sentenced to life imprisonment and solitary confinement, having escaped hanging only by reason of his extreme youth. Within a few weeks he had stripped, trussed up, beaten and otherwise tortured a number of little children. Because of these offenses he was detained in a reform school, but good behavior procured his release after seventeen months. Within the two months following he tortured two more children, bruising, stabbing and otherwise mutilating them until they died. He made several unsuccessful attempts to escape from prison. While he was undergoing penal servitude tales were told of his continued cruelty, and among other accusations was that of catching rats and skinning them alive. These charges were made by persons outside the prison and were never substantiated by the prison officials. Finally, Pomeroy, becoming incensed, brought suit against a woman for $5,000, alleging damage to his reputation. He scored a technical victory—the jury awarded him $1. Though repulsive and asocial, even as a prisoner, he was intelligent. He read extensively, studied law and acquired some knowledge of several languages.

I have elsewhere referred to the following case: A criminal of high intellectual endowment, robust and a writer of note, began to read at the age of 3½ years and entered on a life of crime at 9. He became an inmate of two reformatories, three county jails and a penitentiary. He loved the thrill of stealing and the night after release from a reformatory broke into several houses. Once when arrested there were twenty-nine charges against him, including numerous thefts, kidnaping and sodomy. He said that he was reared by grandparents, was always kindly treated as a child and had attended a private school, a primary school and a college. At 21 he inherited $34,000, which he spent in four years, and later in life he received much financial and other assistance from prominent persons; yet he had no feeling of gratitude and for his crimes no self-reproach. He once said to me: "There is a born criminal and I am one." Nor had he much faith in his fraternity, saying: "There is honor among thieves, is the one good joke accredited to the underworld." With both statements I am in full accord. When last seen, he was 48 years of age. He was at liberty, having been granted a pardon through the intercession of many persons, and was debating whether to return to a life of crime or to accept matrimony from a woman of some culture and means. This man is highly intellectual, but from his own statements and his record of crime he is an amoral imbecile.

Writing of the Englishman, Griffiths Wainewright, under the caption, "Pen, Pencil and Poison," Oscar Wilde said: "Though of an extremely artistic temperament, he followed many masters other than art, being not merely a poet, a painter

and art-critic, an antiquarian and writer of prose, but also a forger of no mean or ordinary capabilities and as a subtle and secret poisoner almost without a rival in this or any age." At 25 years Wainewright had a long and serious period of depression. He was exceedingly sensitive to pain, a marked contrast to his moral insensibility where others were concerned. Being a very sensuous man, he would not live without luxuries. It is not known how the strange fascination of poisoning overtook him, but in some way he had learned of the lethal effects of strychnine. In dress he was dandified; he indulged in perfumes and wore a number of beautiful rings, in one of which strychnine was concealed. DeQuincey said: "His murders were more than were ever known judicially." Through forgery he acquired control of £5,000; the crime was not detected for twelve years. In 1829, having lost their own home through extravagance, Wainewright and his wife were taken into the home of his uncle, Thomas Griffiths. Some time later the uncle died in convulsions and the married couple inherited his property. The second victim was his mother-in-law, Mrs. Abercrombe, who with two daughters had been permitted to live with him. The reason for her murder is not known, but it was thought that she may have acquired knowledge of the dangerousness of his character. Later, Helen, a young and beautiful daughter, died of symptoms similar to those of her mother. She had been murdered in the hope that the £18,000 insurance could be procured, but the insurance companies became suspicious and refused payment. After a delay of five years the case was heard and a decision was rendered in favor of the insurance companies. Feeling unsafe, Wainewright moved to France, where he lived in the home of an old man who was induced to place £3,000 insurance on his life. He died some time later, and though Wainewright did not get the money he felt he had revenged himself on an insurance company. While in France he was detained in jail for some minor offense. Being still wanted in England for forgery, through the arts of a beautiful woman used as a decoy he was induced to return and was arrested. There were five indictments against him, but he was permitted to plead guilty to two, which were not capital in nature. He was convicted and sentenced to transportation for life. While undergoing sentence he would boast of his cleverness as a poisoner and actually made two more attempts to poison persons who had offended him. Havelock Ellis said that Lombroso and others would consider Wainewright a "born criminal" or a "congenital criminal," but he preferred the term "instinctive criminal."

Seemingly as atrocious an intellectual man as ever lived was Gilles de Rais, the original Bluebeard of the Mother Goose story. Born in a French family of high rank and wealth, this iniquitous monster of the fifteenth century had all the educational advantages of that time. He could speak three languages and manifested great interest in military matters. At 16 years he married, the chief attraction being the wealthy estate of his wife's family. She being a relative of the fourth degree, the Church declared the marriage void, a circumstance that did not for the moment disturb de Rais. Becoming disgusted with his wife, he provided for her maintenance in another part of the castle but on learning that she was pregnant and fearing the embarrassment of an illegitimate heir he successfully approached the Church, another ceremony was performed and the difficulty was thus obviated. Unfortunately, the child proved to be a girl, which so angered de Rais that he lost all interest in mother and daughter. In the struggle of Charles VII against England he rendered distinguished service, fighting beside the Maid of Orleans and later, with others, striving hard to disprove the charges that were paving the way to her cruel death. At 25 he had achieved the high distinction of Marshal of France and retired to his estates. At that period those who dared dispute the doctrines of the Church were punished most severely. Many pleasures were denounced as the work of the devil, and their prohibition led to much revolt. It has been believed that these ecclesiastical rigors resulted in the formation of some of the medieval cults, giving rise to devil worship wherein all kinds of pleasures were indulged in and atrocities committed. Books telling of witchcraft, incantations and black magic were freely read. From the undisputed evidence presented at de Rais' subsequent trial, it is believed that he may have belonged

to one of the most sophisticated, licentious and sadistic of these cults. Be that as it may, there is an abundant, well authenticated historic record of the atrocious orgies in which he and others indulged. At 28, after having been away from his estates for some time, he returned and promptly banished his wife and daughter. Then began the dissipation of his vast fortune wherein he vied with the king in the grandeur of his surroundings. Among others who were invited to join him were two priests, one being his cousin. The assemblage then gathered included artists, actors, poets, musicians, designers, illustrators, astrologers, magicians and others. There were a chapel, a choir and also a laboratory for research in alchemy. The castle was surrounded by a big and ferocious guard, while within drinking, carousing and the worst atrocities were being indulged in. Worship of the evil forces called for much human sacrifice. Most of the victims were boys who were trussed up, cut, slashed and otherwise tortured to death. Such iniquities could not go on forever, and the Church finally found him guilty of heresy. The civil authorities then assumed charge and brought him to trial, and it was proved that there had been kidnaped or otherwise enticed to his castles 140 children, though the actual number was believed to be much larger. "De Rais was culpable of crimes so horrible that they could be read in open court only if rendered in the Latin tongue." He made full confession and was hanged, and the body was burned.

Through disease, injury and shock the mind may be strangely affected; this is not recent knowledge, since Oliver Wendell Holmes pointed out that "a profligate mentioned by Plutarch had a fall and struck his head, after which he became a virtuous citizen." Lombroso mentioned several instances: "Gratry, a mediocre singer, became a great master after a beam had fractured his skull. Mabillin, almost an idiot from childhood, fell down a stair-case at 26 years and so badly injured his skull that it had to be trephined; after this he displayed the characteristics of genius. Gall, who narrates this fact, knew a Dane who had been a half idiot, who became intelligent at the age of 13 after having rolled down a stair-case, headforemost. Wallenstein was looked upon as a fool until one day he fell out of a window, and henceforward began to show marked ability."

Several years ago a local surgeon was attempting to increase the cranial capacity of bad boys by means of an incision into the skull; it was his belief that the badness resulted from cramped quarters occupied by the brain. I knew one of his patients, who was twice afterward in the Eastern State Penitentiary and later an inmate of a jail in New Jersey. Apropos of that surgeon's procedure, Dr. Lloyd queried: "Does the good man think he could improve the quality of a nut by boring a hole in its shell?" Another of these boys had headache and a vicious temper and was a truant. The mother said he had once fallen in front of a railroad train and sustained an injury which she was sure had caused his waywardness. A slight depression was evident in front of the skull, and this was thought to be the cause of his delinquencies. Two operations were performed, and soon after he was an inmate of a reformatory, later a county jail and finally a penitentiary. From the last of these institutions he made a sensational escape by burying himself beneath a cartload of ashes; shortly after reaching the streets he arose, phoenix-like, and it was not until six months later that he was apprehended in California. There is a group of children dubbed the "Apache type" who, in the chronic stage of encephalitis, commit a series of misdemeanors, more or less severe. Recently Grossman has recorded the case of a very unruly child who became docile after epidemic encephalitis.

Under constitutional immorality, Tanzi, discussing the type of persons who show the permanent insensibility of ruthless immorality, said: "It is more evident from early childhood, because it is more impressing, notwithstanding the negative nature of its manifestations. In youth, these persons who are immoral through deficiency of sensibility show affection for no one. In their amusements they are placid, silent and cruel. . . . They are not mortified by reproof or humiliated when caught in the act of doing wrong. . . . They neither understand nor value the generous impulses of others; they are skeptical, distrustful and out perfume, so also there are individuals devoid of benevolence and sympathy."
malicious. . . . As there are dogs without the power of scent and flowers with-

There is abundant evidence that the two components of mentality, intellectual and emotional, may not develop harmoniously. One may be greatly in excess and either may show infantilism. Again, disease or injury of the brain may affect one with little or perhaps no effect on the other. Hence, "moral imbecile," "amoral imbecile," "born, congenital, hereditary or instinctive criminal" and "constitutional immorality" are justifiable terms, in the sense that they represent a demonstrable condition, though the designation preferable is debatable.

Browning, in an analysis of 11 cases of cranial trauma followed by serious moral deterioration, but with intellectual integrity, located a "moral center" in the right frontal lobe in right-handed persons. He was convinced that lesions of the first frontal convolution gave rise to irritability, violence and loss of inhibitory power; that lesions of the second and third convolutions gave loss of the "moral sense," leading to absence of shame, fear, sense of duty, etc. Lehman, quoted by Eng, believed the same brain cells can perform the functions of the intellectual and emotional processes. Thalbitzer's hypothesis is that there is a particular emotion center, and with this Eng was inclined to agree. It is suggested by Piéron that undifferentiated emotional reactions may arise at the thalamic level and then be subjected to the discriminating associative intellectual processes at the cortical level.

In regard to a "moral center": Is the cerebral cortex to be regarded as functioning in such a way that local disease or injury could affect its activity only as a whole? Or are there anatomic concentrations, so-called centers, where thought is definitely discriminate, giving such functions as attention, memory, judgment, ideation, special talent and ethical concept? There is definite knowledge of motor centers and knowledge to a lesser extent of those of sensation, speech and the special senses. However, intellectual and emotional centers are not so easily identified, and more data are needed to establish them.

Cystometric Determinations of Intravesical Pressure in Patients with Tumor of the Brain: A Preliminary Report. Dr. James W. Watts and Dr. Charles A. W. Uhle.

The neurogenic bladder associated with disease or injury of the spinal cord is well known by its clinical symptoms and cystoscopic picture. We wish to point out that a neurogenic bladder may be the result of intracranial tumor, presumably through disturbance of the autonomic representation of the bladder in the brain.

In 1927, Rose devised an instrument for measuring intravesical pressure which he called a cystometer. Rose studied patients with various types of lesions in different parts of the spinal cord and believed that a marked deviation from the normal, in the absence of obstructive uropathy or infection, is indicative of a disturbance of the innervation of the bladder. Our own observations on patients with tabes dorsalis and tumor of the spinal cord indicate that the method is valuable for determining the status of the bladder.

We have employed the technic suggested by Muschat and Johnston, which makes use of a simpler and less expensive instrument than that described by Rose. The principle of the determination is the measurement of intravesical pressure in millimeters of mercury. Increasing amounts of fluid are introduced, and the pressure is recorded intermittently after each 50 cc. Attention is paid to the capacity at which the patient has the first desire to void, discomfort and pain of overdistention.

The normal desire to void occurs between a capacity of 75 to 150 cc. The pressure mounts gradually from 0 to 15 or 20 mm. of mercury. As filling continues there is an abrupt rise to between 35 and 50 mm. of mercury at a capacity of about from 300 to 400 cc., when pain may be felt.

In the interpretation of cystometrograms one must be acquainted with the variations which occur in normal subjects. Pathologic changes in the bladder or an obstructive pathologic condition, such as prostatic hypertrophy, may produce a hypotonic or a hypertonic bladder. Mental irritability, lack of cooperation, debilitating and wasting diseases and pregnancy may deviate the curve from normal.

The best results are obtained if the patient is examined in the horizontal position in a quiet room. The examination requires twenty minutes or longer. Rules of asepsis and antisepsis should not be neglected.

Report of Cases.—CASE 1.—B. S., a man aged 27, had symptoms and signs of a tumor of the right temporofrontal lobe. He made no urinary complaints.

A cystometrogram showed a hypotonic bladder. Fluid (650 cc.) injected into the bladder caused (*a*) first desire to void at 100 cc.; (*b*) greater desire to void at 250 cc.; (*c*) pain at 500 cc., and (*d*) leakage about the catheter at 600 cc. The bladder was uninfected. Although sensations appeared at the normal place in the curve, intravesical pressure did not rise above 10 mm. of mercury until 650 cc. of fluid had been injected, when the pressure rose to 40 mm.

A ventriculogram disclosed evidence of a tumor of the right temporal lobe displacing the third ventricle 2 cm. past the midline.

Operation revealed a huge encapsulated glioma of the right temporal lobe.

CASE 2.—S. W. A., a man aged 26, had symptoms and signs indicative of a tumor of the right temporal lobe. Nocturia had occurred two or three times each night since the onset of the illness six weeks before. There was no other urinary disturbance.

A cystometrogram showed a hypotonic bladder. Fluid (700 cc.) introduced into the bladder caused: (*a*) slight desire to void at 225 cc.; (*b*) strong desire to void at 550 cc.; (*c*) no pain, and (*d*) no leakage about the catheter. The highest intravesical pressure during the test was 15 mm. of mercury.

Operation was performed, and an encapsulated glioma of the right temporal lobe was extirpated. The patient recovered.

CASE 3.—J. M. K., a woman aged 22, had symptoms and signs of a tumor of the left cerebellopontile angle. Urinary difficulty and obstinate constipation had been present for two months; later there was retention requiring catheterization. A cystometrogram showed a hypotonic bladder. Fluid (700 cc.) introduced into bladder caused: (*a*) no desire to urinate; (*b*) no pain during the test and (*c*) no leakage around the catheter. The intravesical pressure did not rise above 5 mm. of mercury. The bladder was not infected.

Operation exposed a tumor of the left cerebellopontile angle.

Autopsy showed an acoustic neurinoma, 6 cm. in diameter, compressing the pons and the medulla.

CASE 4.—R. A., a youth aged 19, had symptoms and signs of a tumor occupying the posterior part of the diencephalon and blocking the aqueduct of Sylvius. There were no complaints referable to the urinary tract.

A cystometrogram showed a hypotonic bladder. There was no evidence of an obstructive pathologic condition. Fluid (700 cc.) placed in the bladder caused: (*a*) first desire to urinate at 100 cc.; (*b*) severe desire to void at 500 cc.; (*c*) pain at 700 cc., and (*d*) no leakage about the catheter during the test. The bladder was not infected. The intravesical pressure remained below 10 mm. of mercury until a capacity of 500 cc. was reached, when it rose to 30 cc. at a capacity of 700 cc.; the pressure rose to 40 cc. A ventriculogram revealed a filling defect in the posterior part of the third ventricle, indicative of a tumor in this region.

CASE 5.—D. W., a man aged 64, had symptoms and signs of a tumor of the corpus callosum. He had entered the hospital in the genito-urinary service, with the chief complaint of urinating involuntarily every two or three hours. Under observation, intermittent involuntary emptying of the bladder occurred.

A cystometrogram showed a hypertonic bladder. Fluid (200 cc.) placed in the bladder caused: (*a*) no desire to void and no pain; (*b*) leakage around the catheter at all capacities, and (*c*) no residual urine. The bladder was not infected. The intravesical pressure rose to 60 mm. at 50 cc. capacity, and to over 90 mm. at a capacity of 200 cc. (forcing the mercury over the top of the manometer).

Autopsy showed glioma of the corpus callosum.

CASE 6.—E. M., a youth aged 19, had symptoms and signs of increased intracranial pressure. He had had periodic incontinence of urine for six months.

A cystometrogram showed a hypotonic bladder. Fluid (250 cc.) introduced into the bladder caused: (*a*) no desire to void; (*b*) no pain; (*c*) leakage about the catheter when the capacity of the bladder reached 50 cc., and again at 200 cc.

and 250 cc. After introduction of 50 cc. the intravesical pressure was 60 mm. of mercury; after 250 cc., the pressure was 90 mm. The bladder was not infected.

A ventriculogram showed marked hydrocephalus, with a filling defect in the posterior part of the third ventricle.

Comment.—Clinical observations and experiments on animals support our contention that urinary incontinence and alterations of tonus of the bladder may result from a disturbance of the autonomic representation in the brain. In a recent analysis of the verified tumors of the frontal lobe in this clinic, Dr. Charles H. Frazier found urinary incontinence in 17 per cent of the cases.

In 1873, Ferrier found that stimulation of certain portions of the cerebral cortex led to contraction of the bladder and passage of urine. Three years later, Bochefontaine observed that stimulation of the outer part of the sigmoid gyrus of the dog caused vigorous contraction of the bladder with emptying of the contents. François-Franck and Bechterew likewise obtained contraction of the bladder by exciting various portions of the cerebral cortex, and recently Spiegel and Hunsickor presented evidence for a double pathway, pyramidal and extrapyramidal, from the cortex subserving vesical function. The experiments of Ranson and of Beattie demonstrate the presence of representation of the bladder in the hypothalamus.

Nov. 23, 1934

D. J. McCarthy, M.D., *Presiding*

Choked Disk in Syphilis of the Central Nervous System. Dr. Bernard J. Alpers and Dr. J. C. Yaskin.

The occurrence of choked disk in cases of syphilis of the central nervous system constitutes a practical problem in therapeutics. While it is clear that in the great majority of cases choked disk is due to tumor, it is equally true that there is a small group of cases in which it is due to syphilis. In these cases the condition yields to antisyphilitic treatment as a rule.

We have observed 5 cases of this sort in the past year. In all there were severe subjective symptoms, such as headache, mental confusion, blurring of vision and disturbance of hearing in one or both ears. Headache was by far the most constant and the most disabling symptom. In all the cases there was choked disk of varying degree (from 2 to 6 diopters). In all but 1 case the spinal fluid pressure was definitely elevated (from 20 to 30 mm. of mercury). In 1 case it was 190 mm. of water. The Wassermann reaction of the blood was positive in all cases. The cell count of the spinal fluid was increased in 4 of the 5 cases, the cells being predominantly lymphocytes. In 4 cases also there was a positive Wassermann reaction of the spinal fluid, and all the patients had an abnormal colloidal gold curve of the type typical of syphilis or of dementia paralytica.

Antisyphilitic treatment was followed in all cases by rapid improvement of the subjective complaints, particularly the headache. In 3 of the cases the choked disk disappeared while treatment was being given. In 1 case it was greatly reduced and in another not affected. The type of treatment varied. In 1 instance it consisted of routine weekly injections of mercury and bismuth preparations. In another instance fever therapy was necessary in order to effect improvement. In another instance injections of a soluble bismuth preparation four times a week resulted in the complete disappearance of the choked disk of 5 diopters in thirteen days. Iodides were given in all cases, but no arsenicals were used. In 1 case in which there was no response to treatment a transfrontal craniotomy was performed, and the removal of a chiasmal arachnoiditis resulted in complete relief from headache and disturbance of vision.

Cases of syphilitic choked disk must be diagnosed with caution for it is well known that syphilis and tumor may coexist. Positive serologic tests are not

sufficient, therefore, for a diagnosis of choked disk due to syphilis. The diagnosis is made on the presence chiefly of signs referable to the cranial nerves, often of a widely dispersed nature; on the extreme variability of signs, often from day to day; on the absence of a true localized cerebral process, and on the positive serologic changes in the blood. The pathologic process is probably internal hydrocephalus and syphilitic basilar meningitis, though meningeal signs are not always present clinically. Gumma is rarely the cause of the condition.

The prime consideration is conservation of the eyesight. Treatment must be accompanied by frequent studies of the fundi and frequent examinations of visual acuity. If the latter continues to decrease despite antisyphilitic treatment, decompression must be done to save the eyesight. If, on the other hand, the visual acuity continues unimpaired, treatment may be continued as long as this condition prevails.

DISCUSSION

Dr. Francis Grant: I have a definite feeling about the propriety of reading this paper unless careful attention is called to the fact that syphilis is a rare cause for increased intracranial pressure and choked disk. The common cause for increased intracranial pressure and choked disk is tumor of the brain, and the proper method of treating this condition is surgical exposure. It would be a mistake if the members of this society had gained the impression that choked disk and increased intracranial pressure are due to syphilis and should be treated as syphilis.

Gumma of the brain was present in less than 0.5 per cent of Cushing's series of cases of choked disk. Dr. Alpers quoted Dr. Frazier, stating that he had seen only one massive syphilitic lesion, a gumma, exposed on the operating table. I wish to reiterate and emphasize one point that Dr. Alpers brought out twice: In a case of choked disk with increased intracranial pressure and a positive Wassermann reaction, if it is thought that the patient has syphilis he should be treated accordingly. But treatment should not be continued if after a reasonable length of time, say about three weeks, there is no improvement in the choking, in vision and in the patient's general condition. If no improvement has occurred by that time, one should act on the basis that the patient has a tumor and not syphilis, and the situation should be handled accordingly.

I cannot stress too strongly the point that choked disk is not commonly caused by syphilis or by gumma. If a responsible physician permits treatment for syphilis to be carried to a point where the patient loses vision, he is then responsible for that bad effect, because the treatment for syphilis under these circumstances should not be carried beyond the period required for therapeutic tests.

Dr. William G. Spiller: It seems from the remarks just made that the roentgenographic picture in one of the cases presented was an essential factor in the decision for operation, because of the possibility of finding a parasellar tumor. It has been stated that a thickened arachnoid was found implicating the optic nerves, and the improvement in the condition of the optic nerves is attributed to the incision of this thickened tissue. I understand from Dr. Grant that this is the only case of this character he has had.

Dr. Joseph C. Yaskin: It would be best to answer Dr. Spiller's question. The reason operation was performed in 1 case was because, in spite of regular treatment for ten days, both the subjective symptoms and the ocular symptoms became worse; because of the danger of the patient's losing his eyesight and the terrific headache we thought that it would be safer to be guided by the suggestion made by Dr. Kornblum, that in spite of the presence of syphilis, there might be a parasellar tumor. At the operation Dr. Grant removed the chiasmal adhesions.

In case 3 there were, in addition to headache, jacksonian fits and transitory aphasia. The patient could not utter a sound for several minutes. After the first week of treatment, which consisted of the administration of a mercury preparation, 90 grains (5.85 Gm.) of sodium iodide and injections of a bismuth preparation every fifth day, the headaches and the movements disappeared. The patient still complained of headache, especially in the morning, and careful studies were dis-

couraging. The eyegrounds were getting worse. We did not think that we were dealing with a tumor. We then began a course of fever treatment, and after ten days the eyes showed marked improvement.

I think that Dr. Grant is right in saying that one must be cautious in not overlooking tumors of the brain because patients have evidence of syphilis. Ophthalmologists are frank in saying they are unable to tell in the majority of cases whether the condition in these cases is papilledema or inflammatory papillitis.

Dr. George Wilson: I have had a number of experiences with choking of the disks in cases of syphilis. One was in the case of a man who was injured; in the course of ten days signs indicating involvement of the left temporal lobe appeared. There was choking of 3 diopters in each eye. Dr. Fay operated and found a tumor in the temporal lobe which, on examination, proved to be a gumma. Serologic tests at first, with both the blood and the spinal fluid, were negative. Later they were positive.

Another man in my service had choking of the disks of about 5 or 6 diopters. Dr. Grant saw him for me. The man died before much could be done. At autopsy there were myelitis and basilar meningitis. I wish to ask Dr. Alpers what he thinks is the mechanism of the choking. Is it mechanical or due to a general infection?

Dr. B. J. Alpers: I agree with Dr. Grant that choked disk is usually due to tumor of the brain. I thought that I made this clear in my introductory remarks. In a recent article Greenfield reported 7 cases of syphilitic hydrocephalus in adults, in 6 of which there was marked papilledema; all were cases of syphilitic meningitis.

I believe that the mechanism in the majority of cases is basilar meningitis with resulting hydrocephalus. However, not all the patients are hydrocephalic, and in some instances there may be direct choking of the optic nerves by meningitis around the chiasm. This was the mechanism in case 2 in which operation and removal of adhesions around the chiasm cured the choked disk.

I wish to emphasize that gumma is a rare lesion and in my estimation is not responsible for the syndrome which we have described.

Recurrent Spontaneous Subarachnoid Hemorrhage. Dr. Roy L. Langdon and Dr. Charles C. Cooper.

Recurrences of spontaneous hemorrhage into the subarachnoid space must occur with greater frequency than a survey of the literature indicates. Not only may the diagnosis in such cases be readily overlooked, unless a spinal puncture is performed, but, further, the tendency to spontaneous recovery confuses the completion of accurate diagnosis in many cases in which the patient is not seen until a few days after the onset of symptoms or are not hospitalized for study.

Excepting the instances of subarachnoid hemorrhage occurring as a part of a blood dyscrasia, such as anemia, leukemia and purpura, the etiology depends on the rupture of a vessel damaged by one of five causes: trauma, syphilis, arteriosclerosis, mycotic aneurysms and congenital aneurysmal defects.

Contrary to general expectation, syphilis is not so frequent a cause as might be expected. A careful history will reveal the causal factor at work in cases due to trauma. Among the arteriosclerotic group the general organic health of the patient suggests the possibility of this background, although it must be recognized that there may be advanced cerebral arteriosclerosis out of proportion to that in the general vascular system. It is obvious that the more advanced the age of the patient the more likely is subarachnoid hemorrhage to be associated with acquired constitutional disease. In the mycotic group (Stengel, A., and Wolferth, C. C.: Mycotic [Bacterial] Aneurysms of Intravascular Origin, *Arch. Int. Med.* **37**:527 [April] 1923) careful study will disclose the relationship to a preceding subacute ulcerative endocarditis or vascular lesion.

The most interesting of the groups is that embracing the congenital vascular anomalies, especially congenital miliary aneurysms. This group comprises unquestionably the greatest number of cases formerly considered "idiopathic" and also cases presenting the more frequent recurrences, particularly in young persons.

The case which we present exemplifies this type:

G. K., a woman aged 21, who was admitted to the Germantown Hospital on June 12, 1934, for one week had suffered from severe headache which she had ascribed to the very warm humid weather then prevailing. During this period she continued to work as an operator in a stocking factory. On June 8 (four days before admission), before going to work in the morning, she vomited without nausea, and while at work she lost consciousness. She seemed to sleep throughout that day, mumbling answers to questions when disturbed. She remained stuporous and vomited whenever disturbed until the day of admission. At this time she had severe headache, was semistuporous and was oriented as to place and persons but not as to time. She complained of stiffness of the neck.

Physical examination revealed motor irritability but no convulsions. The patient was mentally lethargic and confused. The head was generally tender to percussion, but no bruit was heard. The blood pressure was 105 systolic and 60 diastolic. There was definite nuchal rigidity, with an increase in the severity of the headache on movements of the head. There was slight cervical adenopathy. The eyes showed no nystagmus; the pupils reacted slowly and equally, although the right was larger than the left. The eyegrounds were normal, and there was no external ocular palsy. The thyroid was slightly enlarged. The thorax and lungs were normal, except for arrhythmic breathing, with occasional sighing expiration. The heart was normal. The abdomen was normal, with the exception of diminution of reflex responses. The muscles of the back were rigid, and there was tenderness over the fourth to the eighth thoracic vertebra. The Kernig sign was present bilaterally. The deep reflexes were at first slightly exaggerated but soon became diminished. Babinski's sign was questionably present on the right. Spinal puncture produced bloody fluid under pressure of 20 mm. of mercury. There was normal response to jugular pressure. The fluid contained 42,000 erythrocytes per cubic millimeter but no organisms, and there was no cultural growth. The chloride content of the spinal fluid was 725 mg. per hundred cubic centimeters. The Kahn, Kolmer and Wassermann reactions of the blood and spinal fluid were negative. The temperature varied from 102 F. on admission to normal on June 19. Roentgenograms of the head and thoracic portion of the spine were normal.

The patient's past medical history, as given by her parents, was of interest. After a normal birth she progressed well until the age of 9 years, when she had an attack similar to the present one with temporary weakness of the right arm. At that time the family lived in Kieselbron, Germany. The attending physician diagnosed the attack as meningitis. Spinal puncture was not performed, and the child recovered in approximately ten days. We were unable to secure further data by corresponding with the physician in Germany. On Oct. 15, 1931, the patient was admitted to the Germantown Hospital with a history of having cried out in acute pain, grasping her head in her hands and falling unconscious. The spinal fluid at that time was hemorrhagic, and a diagnosis of subarachnoid hemorrhage was established. Thirteen spinal punctures were made during that attack, and the patient was discharged fully recovered after three weeks. Preceding admission to the hospital she had suffered from severe headaches and severe dysmenorrhea, with psychic disturbances during the first day of the menses. Gynecological examination showed an infantile type of uterus.

Preceding the present attack she had suffered from headaches for a number of months at intervals of several weeks and on three occasions had had vertigo and had fallen on the street. She had not had visual disturbances.

Comment.—There are only a few cases of subarachnoid hemorrhage with recurrences at long intervals reported in the literature, yet these cases must be frequent in the group of cases of congenital aneurysms because the patients usually have multiple aneurysmal defects and are by virtue of their embryologic deficiency doomed to ruptures of vessels. Russell (*Canad. M. A. J.* **28**:133, 1933) reported 26 cases of subarachnoid hemorrhages in 2 of which there were recurrences; in 1 hemorrhage occurred at the age of 13, and there were 5 recorded recurrences; in another hemorrhage occurred first at the age of 10, with recur-

rences at the ages of 13 and 18 years. Seven of the 26 patients showed aneurysm at the junction of the anterior cerebral and communicating arteries. Symonds (*Quart. J. Med.* **18**:93, 1924-1925) also recorded cases with recurrences.

The frequency of cerebral arterial anomalies has best been shown by Bussé (*Virchows Arch. f. path. Anat.* **229**:178, 1921), who examined the anterior cerebral and communicating arteries in 400 successive cases and found anomalies in 56 per cent and definite aneurysmal dilatations in 10 per cent. Other data on this subject were presented by Keibel and Moll (quoted by Russell: *Canad. M. A. J.* **28**:133, 1933), who demonstrated that embryologically the communication between the two anterior cerebral arteries is a capillary plexus which later forms the anterior communicating artery by the development of one vessel and absorption of others; this explains how in some instances a more or less complicated network may be left. Bussé found remnants of fibrous bands of the earlier network in the walls of the arteries in many cases (76 of 400), giving rise to relative weakness of the walls. The force of the double stream from the two anterior cerebral arteries entering the anastomosing artery with the currents which must be set up, he thought, tends to cause distention of these weakened vessels, producing aneurysms.

Forbus (*Bull. Johns Hopkins Hosp.* **47**:239, 1930) emphasized the independence of development of the muscularis of a major vessel and that of a primary branch, offering this as a probable explanation of the defect of the muscularis and the frequency of bifurcation of the vessels. The fact which he observed, that the two independently developing coats of muscularis fail to fuse completely at the junction of the two vessels, leaving a point of lesser resistance in the wall of the vessel, determines where an aneurysm will be likely to occur and subsequent hemorrhage to follow. It is interesting to note with what great frequency rupture does occur in these cases where a branch is given off from a main vessel or at the junction of the anterior cerebral and the communicating artery or the junction of the internal carotid artery and the circle of Willis, as shown so well by Fuller Albright (*Bull. Johns Hopkins Hosp.* **44**:215, 1929) in his series of cases of aneurysm at that point and his clear description of the syndrome produced by such lesions.

As early as 1859 Sir William Gull (*Guys Hosp. Rep.*, 1859, p. 281) suggested the presence of a congenital aneurysm in some of these cases.

Bagley (Blood in the Cerebrospinal Fluid, *Arch. Surg.* **17**:18 [July] 1928) showed by necropsy observation that spontaneous hemorrhages in infants are usually due to rupture from a congenital persistence of a venous veil or network over the pia.

Retinal hemorrhages may be present in cases of subarachnoid hemorrhage at the base, the cause of which Doubler and Marlow (*Arch. Ophth.* **46**:533, 1917) showed to be due to marked distention of the sheaths of the optic nerve with blood.

Symonds (*Guys Hosp. Rep.* **73**:139, 1923) and Widal (*Presse Méd.* **11**:413, 1903) have described transient massive albuminuria the explanation of which is not clear unless one theorizes as to the existence of a toxic necrosis of the renal tubules, in which case transient glycosuria might be expected, even in the presence of normal blood sugar, owing to the failure of reabsorption of dextrose by the damaged tubules. It is interesting in this respect to note that there was albuminuria in 50 per cent of Russell's 26 cases, casts in 25 per cent and glycosuria in 3 cases, although, as Russell stated, the patients did not have diabetes. At times erythrocytes are present in the urine. Schneider (Thése de Paris, 1910) suggested that these urinary findings may be due to stimulation of Claude Bernard's point in the floor of the fourth ventricle. Russell suggested that it may be due to the sharp rise in blood pressure which these patients frequently show.

Bagley called attention to the fact that clinical manifestations usually precede the large hemorrhages in cases of small cerebral aneurysms, and in the patient presented here such manifestations were present in the instance of the last two attacks.

Further assistance in the diagnosis of the recurrent type may be secured from roentgenograms, which occasionally show a calcified cyst at the point of previous hemorrhage.

DISCUSSION

DR. GEORGE WILSON: I have not observed cases of subarachnoid hemorrhage with so long a period between attacks as that of Dr. Langdon. A patient has just been in my service at the Philadelphia General Hospital with a persistently bloody fluid. It was four or five weeks before the fluid became clear. She remained in a clear mental state. Another case was that of a woman who had a Weber syndrome and died suddenly five weeks later. I wish to second Dr. Langdon's treatment in these cases. Some one said a few years ago that it was murder to perform a spinal puncture in these cases. It seems to me that spinal puncture is the proper procedure.

DR. JOSEPH YASKIN: I have seen 2 cases of spontaneous subarachnoid hemorrhage in which there were convulsions. In these cases spinal punctures were helpful. In 1, the physician was reluctant to perform it. After puncture, the patient improved. I believe that puncture is of definite therapeutic value.

DR. SAMUEL HADDEN: About a month ago a patient was discharged from the Episcopal Hospital who had come in for the third time in two years with hemorrhage. He called me and said, "Doctor, I have that stiffness and I feel nauseated. Can I have a spinal puncture right away?" This patient recognized that a spinal puncture is helpful in cases of subarachnoid hemorrhage.

DR. B. L. KEYES: Do most of these patients die?

DR. R. L. LANGDON: I cannot answer Dr. Keyes from a wide personal experience, but I should say that by virtue of the embryologic defects in the cerebral vessels, which defects are invariably multiple, that these patients are doomed to have recurrences and ultimately to die of such an accident.

In further reference to treatment by spinal drainage, if the patient's coagulation and bleeding time are normal and the spinal fluid is withdrawn slowly by a careful technic with a small bore needle, one should not be terribly concerned about accidents from spinal punctures in selected cases.

THE INTERACTION OF CORTICAL AND LABYRINTHINE IMPULSES ON THE MOVEMENTS OF THE OCULAR MUSCLES. DR. E. A. SPIEGEL and DR. L. ARONSON.

The cortical centers for movements of the ocular muscles were stimulated after unilateral labyrinthectomy, during Bechterew's compensatory nystagmus and during caloric stimulation of the labyrinth (experiments on cats). The interference of the spontaneous nystagmus after loss of one labyrinth, as well as of Bechterew's nystagmus, with cortical impulses which tend to move the eyeballs in the opposite direction eventually results in clonic movements of the eye in the direction of the nystagmus, toward the stimulated cerebral hemisphere instead of toward the resting hemisphere. In caloric stimulation of the labyrinth the vestibular reaction was weaker than the cortical, the corticofugal impulse suppressing a nystagmus toward the stimulated hemisphere. It is assumed that the interference of the corticofugal with the labyrinthine impulses takes place within the vestibular nuclei.

DISCUSSION

DR. ROSS H. THOMPSON: Dr. Spiegel spoke of conjugate deviation of the eyes to the side opposite to stimulation of the cerebral cortex and also of nystagmus as a result of stimulation of the labyrinth. I wish to ask him to explain the anatomic relationship of the mechanisms for the slow and quick components of nystagmus.

DR. E. A. SPIEGEL: By conjugate deviation and cortical reaction I mean the tonic phase when both eyes move to the right side. This is followed by a clonic phase. Both types of movements are conjugating the movement of both eyes in the same direction.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

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A. W. STEARNS, M.D., *Presiding*

ENCEPHALITIS DUE TO EXPOSURE TO TETRA-ETHYL LEAD: REPORT OF A CASE. DR. KARL M. BOWMAN and DR. PAUL HOWARD.

Encephalitis due to tetra-ethyl or tri-ethyl lead is rare; few cases have been reported since the first group of about 70 in 1924-1925. It seems worth while, therefore, to present such a case.

A white man, married, aged 40, was sent to the Boston Psychopathic Hospital on Sept. 12, 1934, by Dr. Joseph Aub, who had made a tentative diagnosis of encephalitis due to exposure to tetra-ethyl lead.

When the patient was admitted to the hospital he was disoriented and confused and had marked disturbance of memory for both recent and remote events, with some tendency to confabulation. He could remember nothing that had happened during the past year. He could not give a correct chronological history of his past life or recall an address or name after one minute. He gave his age as about 37. There was no disturbance of mood, although he seemed somewhat restless, and no special trends were elicited. There was no evidence of delusions or hallucinations. There was no insight, the patient claiming that he was not sick and that his mental faculties were not impaired. The mental picture was that of an impersonal organic psychosis.

Physical examination revealed a man, 5 feet and 10 inches (177.8 cm.) tall. He weighed 147 pounds (66.7 Kg.) and showed evidence of recent loss of weight. He appeared seriously ill. The heart, lungs, abdomen and extremities were normal. The throat was not injected, although the patient complained of sore throat and cough. There was no dehydration. The blood pressure was 110 systolic and 80 diastolic; the pulse rate was 80. Neurologic examination showed a coarse tremor of the hands, arms and head and fine tremors about the mouth. The deep reflexes were equal and active. None of the classic signs of lead poisoning, such as lead line, wrist drop, muscular weakness, colic, anemia or stippling of the red blood cells, were present.

Laboratory tests revealed variable traces of sugar in the urine, with some acetone and the slightest possible trace of albumin. The blood contained 48.4 mg. of nonprotein nitrogen and 141 mg. of sugar per hundred cubic centimeters. The sugar content of the spinal fluid was 110 mg. These deviations from normal disappeared within a few days, and there has been no further evidence of faulty sugar metabolism. Other laboratory tests gave negative results at this time.

Specimens were sent to Dr. Robert Kehoe of the University of Cincinnati Medical School and Dr. Lawrence T. Fairhall of the Harvard Medical School. Dr. Kehoe reported that on September 29 the blood contained 0.15 mg. of lead per hundred grams and that the urine contained 1.13 mg. of lead per liter by the spectrographic method. Dr. Fairhall reported that 2 specimens of spinal fluid were questionable for lead; that a twenty-four hour specimen of feces on September 18 contained 0.3 mg. of lead, a second twenty-four hour specimen on September 24, 0.77 mg., and a third twenty-four hour specimen on September 28, 0.77 mg., and that a specimen of urine of 2,200 cc. on September 26 contained 1.4 mg. of lead, and a second specimen of 4,000 cc. on September 28, 0.19 mg. In these specimens the lead was additionally separated as sulphate and identified positively as lead by microchemical analysis.

The patient is of Scotch-English descent, with no family history of mental or nervous disease or of alcoholism. Birth and early development were normal. He held various jobs and was considered a conscientious and efficient worker. For the year before his admission to the hospital he had worked for an oil company; recently he had cleaned gasoline tanks. In 1923 appendectomy was performed, and

in 1925 he had a light attack of pneumonia. Otherwise there was nothing of significance in the medical history. He married in 1921. In personality, the patient was described as cheerful, energetic, industrious, popular and even-tempered.

The exact details leading up to the illness are not entirely clear. The patient was employed in cleaning gasoline storage tanks. He wore an asbestos suit and a gas mask connected with a pipe line to an oxygen supply. His duty was to remove the crust or scale from the sides of the tanks after they had been emptied. Between August 20 and September 4 he entered 9 gasoline tanks. From about August 21 to 23 he complained that he could not smoke on account of burning in the eyes, nose and throat. He also said that there was something wrong with the air supply in his gas mask. On August 30 headache and insomnia developed. He began to lose weight rapidly and complained of great fatigue. On September 5 he collapsed while at work and was pale but managed to stagger about. He was taken to a general hospital, where he was kept until the next day and then sent home. On September 6 he was perspiring profusely; he had headache and again collapsed. On September 7 he was weak and confused and showed mental symptoms. Insomnia had continued throughout this period. On September 8 he was very restless. On September 9 restlessness continued, and he showed marked impairment of memory. This picture continued until the time of admission to the Boston Psychopathic Hospital.

After admission the patient grew rapidly worse. He began to sweat frequently and profusely. He would lie on the bed, rolling his head back and forth in a fashion sometimes seen in cases of rickets. The temperature, which was normal on admission, rose to 102 F., and the white blood cell count, which was 6,400 on admission, rose to 18,000. The patient became practically comatose, and there was absence of reflexes. There were an area of hyperesthesia in the lumbar region and vague general abdominal tenderness. The only signs elicited in the chest were that the breath sounds were heard better on the left side than on the right. This condition soon disappeared. The temperature fell by crisis. The sensorium began to clear, and memory gradually improved. On October 5 the patient was able to go to the convalescent ward. His memory showed steady improvement from day to day; it was fairly good for past events but poor for recent ones. He could not remember at any time having worked at cleaning gasoline tanks. This improvement of intellectual function has continued fairly steadily until the present, so that now the patient has a fair memory for current events and for his past life. He still has difficulty in recalling events of two or three weeks previously and has not regained memory of his work in the gasoline tanks. Some slight stippling of the blood cells appeared late, but this was not regarded by Dr. Aub as sufficient to be diagnostic. On October 29 it was discovered that secondary anemia had developed. The hemoglobin content was 76 per cent (Sahli). The red blood cells numbered 3,580,000, and the white blood cells, 19,000. At the same time a cough developed. Examination of the sputum and roentgen examination of the lungs showed findings which were considered difficult to interpret but were consistent with those obtained in cases of bronchopneumonia. Repeated examinations of the sputum have revealed no evidence of tuberculosis. The fever has gradually subsided. There are practically no pulmonary signs except that the breath sounds are heard much more distinctly on the left side than on the right. A recent roentgenogram showed practically the same picture as before. Dr. Coffin of the Boston Psychopathic Hospital and Dr. Sosman of the Peter Bent Brigham Hospital are not satisfied that the condition is simple bronchopneumonia. The treatment in this case has consisted in forcing fluids and the use of compounds of light metals, such as calcium and magnesium.

It is well recognized that tetra-ethyl lead may produce encephalitis and that mental symptoms form a prominent part of the picture. When the first cases were reported in New Jersey in 1924, ethyl gasoline was called "looney gas." The symptoms in order of frequency are: insomnia, lowered blood pressure, subnormal temperature, anorexia, nausea, bodily weakness, abdominal cramps, unaccustomed or annoying dreams, decided loss of weight, slow pulse, headache and tremors. Kehoe reported a series of cases in 1925 in which he emphasized that the clinical

picture is different from that usually seen in cases of lead poisoning. He stated that stippling and lead line occur only infrequently and not early in the disease and that the mode of entrance is by inhalation or directly through the skin. He stated that in some cases the mental picture resembles that of delirium tremens, the patient being overactive and overtalkative and suffering from hallucinations. It is generally agreed that tetra-ethyl lead combines more readily with nerve tissue than do other forms of lead; hence a sudden attack of lead encephalitis is liable to occur without the ordinary signs of chronic lead poisoning. Kehoe reported in 1934 that tri-ethyl lead may be inhaled in the form of finely divided dust by workmen cleaning the interiors of gasoline tanks, with absorption of lead and acute intoxication following. He stated that the tetra-ethyl lead which is left on the sides of the tank decomposes after long standing to form crystalline tri-ethyl compounds. Apparently the clinical picture from tri-ethyl lead is similar to that of tetra-ethyl lead, and on the basis of Kehoe's report it seems that my patient had been exposed to tri-ethyl lead rather than to tetra-ethyl lead.

DISCUSSION

DR. JOSEPH AUB: It is important to remember that the whole picture of poisoning from organic lead compounds is entirely different from that of poisoning by inorganic lead compounds. The peripheral manifestations seem to be largely lacking, and lead colic and wrist drop do not seem to occur, while stippling in the blood cells appears only long after the acute cerebral abnormaltitis produced by these organic compounds. Kehoe has shown that after a few days the distribution of the lead from tetra-ethyl lead does not differ from that of inorganic compounds, but Gettler was able to find tetra-ethyl lead in the brain in a patient who died of poisoning from this compound. Considerable quantities of lead were isolated from the urine of the patient under discussion, showing that he had absorbed toxic amounts of some lead compound. While I have heard of other patients with severe mental disturbance such as this patient showed, most of those I have seen before have had only mild delusions; this patient stands out as unique in my experience because of the severity of the symptoms and the recovery.

DR. ALICE HAMILTON: I first heard of tetra-ethyl lead in 1922. An expert from the du Pont Company described to me an acute cerebral form of plumbism which was not encephalopathy, as it is known, but resembled delirium tremens; he said that they held the ethyl radical responsible, not the lead. A little over a year later the situation became a matter of sensational publicity when 28 severe cases occurred in New Jersey in the du Pont works and in the Standard Oil works, where the compound was produced. The health services of several states threatened to forbid the use of ethyl gasoline. The story crossed the ocean; questions were asked in the British Parliament, and Switzerland forbade the importation of ethyl gasoline. It was not so much the danger to the makers and blenders that aroused this excitement but the fear that the lead discharged from motor engines might be a danger not only in garage work but in the streets, for in the course of combustion tetra-ethyl lead is changed to the chloride or bromide (according to the "carrier" used), both of which are unusually toxic compounds and are discharged in the exhaust gas. These public protests moved the purveyors of ethyl gasoline to ask the United States Public Health Service for a scientific study of the possible danger to the public, and this was done. The service attacked the problem in a practical way. They examined five groups of men: (1) taxi drivers who had never used lead gasoline, (2) taxi drivers who had used it for two years, (3) mechanics in garages where it had never been used, (4) mechanics in garages where it had been used for two years and (5) a control group of workers on storage batteries who were exposed to a known lead hazard of unusual severity. The investigators found what they considered evidence of lead poisoning only in the control group and evidence of lead absorption in the fourth group but not in any of the other three. Kehoe, of Cincinnati, and his colleagues had previously made a similar study of attendants at filling stations and garage mechanics and

had come to the same conclusion. The United States Public Health Service then announced that there was no reason why ethyl gasoline should not be put on the market. Some time later a British Royal Commission examined these findings and confirmed them. The United States Public Health Service has ordered the labeling of all pumps delivering ethyl gasoline and has arranged with the purveyors for an investigation of every case of supposed plumbism resulting from contact with it. Leake, of the United States Public Health Service, and Kehoe, of Cincinnati, have followed up all these cases, and in 1932 I was told by the former that 94 illnesses in 72 persons had been investigated but in none was lead found to have played a part. The present case belongs in the category of the early cases and is for that reason an interesting rarity, for under present conditions one would look for such acute poisoning only as the result of unusual combination of circumstances.

DR. W. WEIGNER: Was an examination made of the spinal fluid, and was lead found?

DR. P. HOWARD: There were insignificant amounts in the spinal fluid—less than 0.01 mg.

DR. H. R. VIETS: Were there any signs of increased intracranial pressure either in the eyegrounds or elsewhere?

DR. P. HOWARD: There was no increase in intracranial pressure; the eyegrounds were normal.

DR. H. R. VIETS: The fact that there was no increased intracranial pressure differentiates this type of encephalopathy due to lead from the ordinary type. The pressure is often greatly increased in the former, particularly in children. Some patients have been operated on for supposed cerebral tumor.

DR. W. BLOOMBERG: I wish to ask about the suit and mask that the man wore?

DR. P. HOWARD: The man did not recall anything about it. The history of this was secured from the wife. There has been no official report made by the company. The man wore an asbestos suit, but there was no irritation of the skin, so I do not think there was absorption by the skin. He did complain of the air in his gas mask, and it was probably, therefore, an absorption by inhalation.

CEREBRAL CHANGES IN GASTRO-INTESTINAL INFECTIONS WITH TERMINAL CACHEXIA AND THEIR RELATION TO PHYSICOCHEMICAL PROPERTIES OF THE BRAIN. DR. LEO ALEXANDER.

The first part of this paper summarizes studies which have been done at the Peiping Union Medical College, in part in collaboration with Dr. T. T. Wu (*Chinese M. J.* **48**:1, 1934; ARCH. NEUROL. & PSYCHIAT. **32**:933 [Nov.] 1934; **33**:72 [Jan.] 1935). Three sets of changes were found in these studies: (1) vascular lesions, indicating circulatory failure as the ultimate cause of death; (2) disseminated parenchymatous and glial changes, the etiology of which cannot yet be satisfactorily interpreted; (3) a diffuse physicochemical change, which finds its expression in (*a*) pseudo-atrophy, (*b*) alteration of the water-binding capacity of the brain tissue, as expressed by the rate of swelling in various solutions of salt, acid and alkali, and (*c*) a peculiar alteration of the attitude of the tissue toward silver salts, which has been observed already by other authors but hitherto has been interpreted as analogous to senile cellular changes. A similar change could be produced experimentally by soaking fresh human brain tissue in water or salt solutions before fixation.

Further studies on the physicochemical properties of the brain and their relationship with the neurofibrillar impregnation were done at the Worcester State Hospital, in collaboration with Dr. Joseph M. Looney. The publication of these studies is in preparation. We determined in our cases: (1) the differential ratio of the capacity of the skull to the volume of the brain; (2) the differential ratio of the capacity of the skull to the weight of the brain; (3) the specific weight of the brain; (4) the total water content of the gray matter; (5) the total water

content of the white matter; (6) the water-binding capacity and the maximum shrinking of the brain tissue in various salt solutions; (7) the slope of the curve of water absorption, as indicated by the time required to reach a certain level, and (8) the p_H of the tissue.

Our results may be summarized as follows: (1) High values of water content of the white matter are found in swollen as well as in atrophic brains, while the lower and middle values are found among brains with about normal differential ratio; (2) the water content of the white and that of the gray matter are not correlated, which is well illustrated also by the fact that in edema of the brain only the white substance swells, while the breadth of the gray remains normal or appears even somewhat narrower in a transverse section; (3) the water absorption capacity is higher in swollen brains and is diminished in atrophic brains; it is also relatively diminished in the atrophic areas in cases of focal atrophy; (4) the maximum shrinking of brain tissue and the "preabsorption time" are correlated; (5) atrophic brains frequently show a diffuse "soaking change" on silver impregnation, besides other structural abnormalities; (6) the hypothesis is presented that senile atrophy of the brain may in part also be "pseudo-atrophic," i. e., due to an alteration in water-binding capacity of the tissue.

DR. T. J. PUTNAM: This presentation opens many views. It illustrates how the investigation of a special minor point may generally expand into generalizations of wide bearing. One begins with neuropathologic considerations and ends with fundamental chemical and neuropathologic considerations. One cannot help speculating what the actual substances are that take the silver stain. In general, it can be said that they are all silver precipitants, and there must be a variety of them. At the same time the variety must be limited in the tissue in question, since not all elements stain. I wonder if Dr. Alexander can shed further light on this subject.

DR. WILLIAM HUGHES: Were there any changes in the retina?

DR. ROY HOSKINS: May not the changes in staining be due to changes in the state of colloidal aggregation. I wish to ask Dr. Alexander how far he got in a consideration of the p_H? Martin Fischer worked along this line and laid a great deal of stress on it. The p_H of the tissues would make a great deal of difference in hydrophilic properties.

DR. L. S. KING: In view of the capriciousness of the Bielschowsky stain, how accurately controlled were the impregnations of the pathologic material as compared with those of the normal material?

DR. L. ALEXANDER: Retinal changes in similar conditions, together with keratomalacia, were described by Dr. Arnold Pillat in Peiping. Some of the children among our subjects were also his patients.

Dr. Hoskins' conception that changes in the state of colloidal aggregation and of p_H may be the underlying cause of alterations of the hydrophilic properties of the tissue as well as of many changes in staining has been a working hypothesis in this study; it is, however, difficult to prove in human autopsy material. So far we have 1 definite observation in this line. A man who died of lye poisoning showed at autopsy a severely swollen, edematous brain (the differential ratio between the capacity of the skull and of the brain was -1.07) and a highly increased water-binding capacity of the tissue; the tissue continued to swell even when incubated in a 10 per cent saline solution. The p_H of the brain tissue was alkaline, namely, 7.19. In this case the relation between edema and alkalinization appears obvious.

In our studies on the "soaking change" as demonstrated by Bielschowsky's silver impregnation of neurofibrils we always used the same technical procedures on control material that we used on pathologic material. The specimens were always stained at the same time and remained exactly the same length of time in the different reagents, which were prepared at the same time in large jars and then divided into equal portions. Exactly the same technic was applied to all specimens. Thus, in our studies the Bielschowsky stain lost much of its

capriciousness, which we consider to be due largely to the influence of the ultimate systemic disease, with edematous conditions, emaciation, dehydration, terminal cachexia and long agony, and of postmortem changes. Therefore, any specimen showing neurofibrillar changes together with argentophilia of the nuclei, a picture which we described as "soaking change," should be interpreted with great precaution, and its relation to the aforementioned factors should be considered.

Dementia Paralytica: Results of Treatment with Tryparsamide. Dr. Harry C. Solomon and Dr. Samuel H. Epstein.

This article was published in full in the June issue of the Archives, p. 1216.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Nov. 15, 1934

Theodore T. Stone, M.D., *President, Presiding*

Subacute Combined Degeneration of the Spinal Cord with Epidural Hemorrhage. Dr. George B. Hassin and Dr. Theodore T. Stone.

This paper will appear in full in a later issue of the Archives.

Some Functions of the Hypothalamus. Dr. S. W. Ranson.

The hypothalamus is the part of the brain responsible for the elaboration and execution of the complex reaction pattern characteristic of intense emotion. With the use of cats it was found that rapid respiration, dilatation of the pupils, erection of hair and constriction of the blood vessels, with a resultant rise in the blood pressure, which form parts of this pattern, can be induced by electrical stimulation of the hypothalamus. After several seconds the excitation caused by continued stimulation spreads to the somatic motor centers and causes the cat to lash its tail, claw at the hammock in which it is restrained and struggle violently to free itself. This is in harmony with the observations of Bard, who showed that when the cerebral hemispheres and thalamus of a cat were removed, leaving in place only the hypothalamus, the animal showed all the signs of rage on the slightest provocation, but if the hypothalamus was also removed the cat was incapable of anything approaching emotional behavior.

Prolonged somnolence can be produced in cats and monkeys by lesions in the hypothalamus, and animals, when they recover from this somnolence, show a remarkable decrease in emotional excitability. Monkeys which before the operation were wild and exceedingly difficult to handle became tame and tractable. The complete loss of fear and the change from a mild monkey into a pet was a remarkable transformation.

It is not surprising, in view of the signs of emotional excitement caused by stimulation of the hypothalamus, that its partial destruction should cause dampening of emotional expression. This change in behavior appears to have been due to impairment of the hypothalamic mechanism concerned with the coordination and integration of emotional expression.

Physicians have known for years that damage to the hypothalamus often causes prolonged somnolence in man, and it has now been shown experimentally that sharply circumscribed injuries in this region have this effect also on cats and monkeys.

It is difficult to understand why an injury to the hypothalamus which does not interrupt any of the great sensory pathways to the cerebral cortex should produce sleep. It seems probable that the explanation may lie in the relation of this part of the brain to the emotions.

The excitation caused by stimulation of the hypothalamus was found to reach the sympathetic and then the somatic motor centers, producing widespread activation of both smooth and skeletal musculature. The result was a thoroughly excited animal—just the reverse of the condition which exists in sleep. From the work of Bard it is known that the hypothalamus can produce this widespread excitation after every part of the brain in front of it has been removed. It is capable of keeping the body in an excited state independently of the cerebral cortex. In view of these facts it does not seem unreasonable to attribute the somnolence seen in these experiments to impairment of this mechanism and to think of the hypothalamus as playing through its emotional drive an important part in maintaining the waking state.

DISCUSSION

DR. PERCIVAL BAILEY: Dr. Ranson said nothing about any movements of the uterus provoked by stimulation of the hypothalamus. Has he made any observations of such movements? I wish to inquire also whether he has made observations concerning the cells of origin of the median bundle of the forebrain. Dr. Ranson implied, in quoting Dr. Bard, that the cerebral cortex was the seat of consciousness. Does he believe that the nervous mechanism concerned with consciousness is situated in the cerebral cortex? In my experience a small lesion in the region of the midbrain is more apt to arrest consciousness than in any other area of similar size in the nervous system.

I wish to know also whether Dr. Ranson has made studies of retrograde degeneration which might indicate the origin of the fibers the destruction of which causes the symptoms which he has described. I am thinking of a possible relationship with area 6 or with other cortical areas which have been shown to have connections with the sympathetic motor centers.

DR. CHESTER DARROW: I wish to ask Dr. Ranson whether he noticed any vasomotor and secretory disturbances, especially in the pads of the cats' feet, in the cataleptic stage. Also, if he conceives that the changes seen in animals with hypothalamic catalepsy, such as forced grasping, are definitely associated with the similar syndrome reported by Fulton, Jacobsen, Richter and others after extirpation of the premotor area?

DR. R. L. JENKINS: In his book on epidemic encephalitis, von Economo sought to differentiate between body sleep and brain sleep. He described what he conceived to be a state of dissociation of the two, wherein the patient would be awake in the morning hours but sit immobile, be awake and active in the afternoon, go to sleep but toss restlessly in the early part of the night and then calm down and sleep quietly until morning. He suggested that there are two separate centers for what he called brain sleep and body sleep. I wish to ask Dr. Ranson if he noticed any disturbances of motility like this or has any reflections on the subject.

DR. PAUL C. BUCY: In view of the fact that Dr. Ranson has been able to induce hypersomnia by destructive lesions of the hypothalamus, I wish to ask if he has been able to correlate his work with that of Dr. Hess, of Zurich, who induced sleep by stimulation of nuclei in this general region.

I believe that Dr. Ranson would agree that there is evidence, particularly in the work of Dr. Philip Bard, that the sympathetic activities of the hypothalamus are not independent of the cerebral cortex but rather that the cortex exerts an inhibitory influence over these functions. I wish to ask if Dr. Ranson has any information as to what part of the cortex may be so concerned. Recently there have appeared reports of work from Dr. Fulton's laboratories indicating that the premotor cortex is concerned, at least in part, with sympathetic nervous activity. In view of the facts that Dr. Ranson has been able to produce forced grasping by making lesions in the hypothalamus and that forced grasping also appears after destruction of the premotor cortex, it seems plausible that fibers from the premotor area pass through the hypothalamus and may therefore be concerned in its sympathetic activities.

I wish also to ask Dr. Ranson whether he believes there are centers in the medulla oblongata concerned with vasomotor phenomena to which some fibers from the hypothalamus pass. In view of his work on this point a number of years ago, I am sure that he has considered it.

DR. S. W. RANSON: In reply to Dr. Bailey's questions, the uterus has not been observed—only the bladder, the blood vessels and, under the fluoroscope, the gastro-intestinal tract.

My associates and I have not done anything with the cells of origin of the median bundle of the forebrain. It is believed that the bundle has a rather wide origin in the rostrally placed olfactory centers, Something might be done to elucidate this problem by the method of chromatolysis, but we have not attempted it. Neither have we made any studies with the Marchi method as to where the tract terminates, which is an obvious thing to do. We know that the median bundle of the forebrain as such is not the structure that is responsible for the reactions. Farther forward, in front of the optic chiasm, stimulation of the median bundle of the forebrain is quite without effect on respiration, blood pressure or contraction of the bladder. I do not know whether sympathetic centers or only sympathetic fibers are being stimulated. I can see that it is possible, although there is no anatomic confirmation of it, that fibers arising in the cell groups in the median part of the hypothalamus may pass into a descending tract in the lateral part and there be affected by the stimulaton.

In my statement that Bard's removal of the cerebral hemisphere eliminated all possibility of conscious anger in his hypothalamic cats, I did not mean to imply that the cerebral cortex is the exclusive seat of consciousness, but that it is such an important part of the neural mechanism involved in consciousness that its removal is generally believed to eliminate consciousness entirely.

I cannot answer Dr. Darrow's question about secretory disturbances in the cataleptic state. It is difficult to detect changes in sweat secretion without elaborate methods, because the sweat dries so rapidly. There is, however, evidence that there is some vasomotor change in the form of dilatation of the cutaneous vessels. As to the matter of forced grasping, the monkey has a pronounced grasp reflex, which is important for arboreal life. The question may arise whether forced grasping in the monkey may not appear in a variety of conditions. I would not be prepared to go so far as to say that forced grasping in these somnolent monkeys was evidence that fibers from the frontal cortex pass through the hypothalamus. Forced grasping is produced by lesions of the cortex, and it is also produced by the hypothalamic lesions which cause somnolence.

Dr. Jenkins brought up the question of body sleep and brain sleep. My idea is that the lesions in the cataleptic animals destroyed the mechanism in the hypothalamus which is responsible for emotional drive. Stimulation of the hypothalamus causes widespread excitation both of visceral and of skeletal musculature. Interruption of the descending tract from the hypothalamus removes this drive and permits relaxation of the body. Complete relaxation tends to produce real sleep.

There is a definite change in motility—a marked inertia. It is hard to get these animals to move. Usually they will move only if forced to do so, but if they are pushed off the table they will alight on their feet. There was one cat in the series used for the experiments that was interesting. A white rat was moved back and forth in front of this cat as it sat on the table, and it was some little time before it paid any attention to the rat. Then it made a spring at the rat and the two went off the table to the floor, the cat landing on is feet. It stood there with the rat in its mouth for about ten minutes and then dropped it.

Dr. Bucy raised the question of the relation of our work to that of Dr. Hess. Dr. Hess produced somnolence by passing a peculiar type of electric current through the basal ganglia, and I do not know how far the somnolence was due to the type of current used. His illustration showing the location of the electrodes in successful experiments shows that the effect could be obtained from various widely separated and functionally distinct regions of the brain. In our experiments, stimulation of the hypothalamus of cataleptic animals in the ordinary way with

a faradic current produced the reverse of sleep—widespread excitation of visceral and skeletal musculature—and in the waking animal it produced all the signs of intense emotional excitement.

I am not sure just how far the hypothalamus is under the control of the cerebral cortex. A great deal more work needs to be done before their interrelationship is properly understood.

The diagram of the descending tract from the hypothalamus did not show the vasomotor center in the medulla, but that was because in the interest of simplicity all details were eliminated from the diagram.

UNUSUAL TUMORS OF THE PINEAL BODY. DR. HOWARD ZEITLIN (by invitation).

This article will appear in full in a later issue of the ARCHIVES.

Book Reviews

Nouveau traité de psychologie. Volume III. Les associations sensitivo-motrices. By Georges Dumas, in collaboration with André Ombredane. Price, 100 francs. Pp. 462, with 155 illustrations and drawings. Paris: Félix Alcan, 1933.

The greater part of this volume is devoted to a subject in which Dumas is particularly interested, the expression of emotions. He reviews the literature on this problem and the various methods of attacking it. Among the latter he finds the study of psychotic patients most profitable and illustrates the various emotional expressions by numerous photographs of patients showing different types of mental disorder.

Dumas is also responsible for another section of the volume, that on mimicry, with a chapter on vocal mimicry. The literature on this subject is much less extensive than that on the expression of emotion, but the subject is of great interest, particularly in connection with any study of language and its disorders.

Ombredane contributes two ably written sections, a comparatively brief one on equilibrium and orientation and a longer one on language. The greater part of the latter is concerned with aphasia, apraxia and agnosia. Ombredane was a student of Foix, and his views on these subjects follow those of Foix and Marie, for the most part. He has also been greatly influenced by Jackson's work, however, and particularly by Jackson's concept of the disturbance of the higher language functions, with the persistence of the inferior and more automatic. Ombredane gives interesting critical discussions of Head's work on aphasia, but does not recognize the many recent German contributions, notably, those by Goldstein, Isserlin, Kleist, Robert Klein and Johannes Lange. This neglect is the chief adverse criticism of his work as a historical survey.

He is apparently much interested in the work of Pavlov, and his original contribution is chiefly an attempt to apply what is known of facilitation and inhibition in cerebral functioning to the phenomena of aphasia, apraxia and agnosia. The attempt is decidedly worth while, but it is clear, as Ombredane himself would agree, that comparatively little is yet understood about the functional basis of any of these disorders. Their complexity and diversity are such that an unqualified acceptance of Jackson's principle of the preservation of the simple and more automatic responses, to which Ombredane wholeheartedly subscribes, is dangerous. Ombredane's descriptions of aphasic behavior include many excellent examples to support Jackson's principle, but other examples might be cited in which the more automatic responses show relatively greater disturbance than the higher and more complex.

Book Notices

Human Heredity. By Erwin Baur, Eugen Fischer and Fritz Lenz. Translated by Eden and Cedar Paul. Price, $8. Pp. 734, with 172 illustrations and 9 plates. New York: The Macmillan Company, 1931.

The German original of this work is entitled "Menschliche Erblichkeitslehre," and a third edition was published in Munich in 1927. The translation was made from that edition by Eden and Cedar Paul, but with supplements and corrections supplied by the authors during the preparation of the English version. This is an important work, previous editions having been published years ago and a second edition having been published in 1923.

Some additions to previous editions are presented in this volume in certain sections. The first section, "Sketch of the General Theory of Variation and Heredity," is by Dr. Erwin Baur. The second section, "Racial Differences in Mankind," is by Dr. Eugen Fischer. The last three sections "Morbific Heredity Factors"; "Methodology," and "The Inheritance of Intellectual Gifts," are all by Dr. Fritz Lenz. The work is too involved and too detailed to be reviewed specifically. It is sufficient to say that it seems exact, clearly presented and unusually detailed. The illustrations, figures and plates are numerous, making the subject matter much less difficult. The variations in individuals and races in regard to the hereditary transmission of disease and the methods of study of heredity are treated fully. An especially interesting chapter is the one on racial psychology. Deeply interesting are the sections on the inheritance of talent and their relation to psychopathy.

This is a monumental work in every respect and is of value for graduate rather than for general students. The index in both German and English is complete. A complete bibliography is also included.

The Patient and the Weather. Volume II. Autonomic Disintegration. By William F. Petersen, M.D., with the assistance of Margaret E. Milliken, S.M. Price, $6.50. Pp. 530, with 249 figures and charts. Ann Arbor, Mich.: Edwards Brothers, 1934.

This volume is the second on a study of the effect of environment on the organism. It is concerned first with certain general considerations and then with more specific problems, such as gastric ulcer, the neuroses, the urticarias, asthma, glaucoma, arthritis and other diseases. Its object is to show the effect of temperature on the organism under certain conditions of health and disease. This is done chiefly through the method of the study of cases.

The book is rather peculiarly constructed, with double columns and with a mimeographed appearance. The subject is a much neglected one and is probably of some importance, but it would be more desirable for persons who know nothing about this problem to have more cleancut conclusions concerning the various effects of weather on the patient.

The Wistar Institute Style Brief. Prepared by the cooperative efforts of the editors of journals published by the Wistar Institute and the staff of the Wistar Institute Press. Price, $2. Pp. 170, with 23 text figures and 37 plates. Philadelphia: Wistar Institute of Anatomy and Biology, 1934.

This book is a guide for authors in regard to the preparation of manuscripts and drawings for the most effective and economical publishing of reports of biologic research. One cannot speak too highly of the merits of this outline. In it there are considered opinions relating to the mechanical preparation of manuscripts and drawings for the printer and engraver, as well as the relative costs of the various methods of producing tables and illustrations. This brief should be an excellent aid not only to inexperienced authors but to the experienced as well.